THE PRACTITIONER

No. 1120 October 1961 Volume 187

THE MONTH

The Symposium

IT is a sign of the times that three of the contributors to our annual Special Number on 'Advances in Treatment' this year do not concern themselves with 'treatment' in the narrow sense of the term. The contributors in question are those dealing with advances in pædiatrics, general practice, and public health. In the case of the last of these—public health—the reason is perfectly obvious, but the important point is that by the inclusion of this subject in such a Special Number it is recognized that preventive medicine is an integral part of the practice of medicine. The reasons why the other two subjects have been approached in this modern style are best given by the contributors themselves. 'The holistic conception of child life within the family circle', according to Professor W. S. Craig, 'is fundamental to pædiatric thought, and a knowledge of human relations, and of the art of consultation and physical examination, must continue to provide the foundations of pædiatric teaching'. 'Too often', according to Dr. Richard Scott, 'advance is halted by our failure to apply existing knowledge. It would appear that as in many other spheres so also in medicine are we more skilful in advancing knowledge than in applying it'.

This broader outlook in the interpretation of 'treatment' is a welcome sign of how clinicians are adapting themselves to the changing outlook in medicine. That 'treatment' in the narrower sense of the term is not being overlooked is well exemplified by the other fifteen articles in the symposium.

Labelling Alcoholic Liquors

THE labelling of alcoholic beverages in this country is just about as archaic as it could be. All that the labelling of Food Order, 1953, does is to stipulate the proof standard for spirits and fortified wines. How many consumers of alcoholic liquors know that '70° proof' whisky and gin contains approximately 40 per cent. alcohol by volume? The position is even more absurd in view of the fact that in Britain pure alcohol is 175° proof, on the Continent pure spirit is 100° proof, whilst there is yet a third standard of proof spirit in the United States. The time has clearly come when, as Guy Bousfield contends in the summer issue of *Health Horizon*, 'all alcoholic beverages containing over a small amount of spirit should be clearly marked with the approximate percentage of alcohol by volume which they contain'.

The confusion that may arise is well exemplified in the case of beer. As Dr. Bousfield points out, 'even experienced drinkers often do not know that a pint of good bitter beer contains about as much alcohol as a double

whisky'. Another example he quotes is that of a certain 'bottled strong ale': no-one who has drunk three half-pint bottles of this ale 'in a reasonably short time should try to handle the controls of a car. Yet, to the unwary, one-and-a-half pints of beer does not sound an excessive intake'. Equally relevant is his rider: 'There is one brand of cider in particular which can prove just as dangerous'. Granted that the amount of alcohol is not the sole factor in determining an individual's capacity to drive. Factors such as the oil of wormwood in absinthe, for example, undoubtedly play a part. In addition, much of the beer in this country is drawn direct from the barrel. On the other hand, if all but the weaker alcoholic drinks were clearly labelled with their approximate percentage of alcohol by volume, the alcohol-consuming section of the population would be able to gauge more accurately than they can at the moment, how much alcohol they are imbibing on any one occasion. The effect, especially upon standards of driving, could be nothing but beneficial.

Hebridean Practice

THE practice of medicine in the Outer Hebrides would still appear to be a challenge to the young practitioner with initiative, stamina and a real love for his profession. Such at least is the impression the reader obtains from an account by Dr. H. Stuart Patterson, an Australian general practitioner, of a locum he did in the Isle of Lewis (*Ann. gen. Pract.*, 1961, **6**, 7). The waiting-room was 'so cheerless a place that the doctor's housekeeper invariably took the patients through her kitchen and sat them in the doctor's dining room in which a fire was usually burning summer as well as winter'. The consulting room was 'as cheerless a place as the waiting room'. The branch surgery, ten miles farther north, was equally spartan: 'It contained nothing but a table, two kitchen chairs, wash hand basin and examination couch. The floor was without even linoleum'. As Dr. Patterson comments: 'My principal was a real Spartan'. 'He was, however', he adds, 'one of the kindest and most thoughtful of men'.

Perhaps the most depressing picture is of the conditions in some of the old cottages, or 'black houses' that still exist, as the following vivid pen picture shows. 'I shall never forget going to see one old man dying of congestive cardiac failure who lived in one of these primitive houses. There he was in a large brass double bed in one corner of the dark room, in a uriniferous all-pervading odour and leaning forwards intermittently and spitting on the earth floor'. Professionally what interested the locum from 'down under' was 'the prevalence of hypertension from which a very large proportion of the doctor's patients over the age of 40 appeared to suffer' and the fact that 'the teeth of the islanders were also appallingly bad'. What will be of equal interest to his British colleagues will be his comment: 'Much of my time was taken up with issuing National Health Sickness Certificates and, what with "bad backs" and hypertension, almost a third of the patients appeared to be supported by a benevolent Government'.

Medicinal Cloves

In the spirit of the old adage it is only fit and proper in a Special Number devoted to 'Advances in Treatment' to cast an eye backwards over the history of one of the oldest drugs in the pharmacopœia—cloves. An opportunity for such an exercise is provided by an admirable review by George R. Beattie of 'The fragrant clove' (*Soap, Perfumery and Cosmetics*, 1961, **34**, 541). Like everything venerable in medicine it dates back to the 'Father of Medicine', and is to be found among the Hippocratic 400 'simples'. The earliest English reference to it appears to be in a 13th century encyclopædia, in which the monkish author notes that cloves 'have manifold virtues, being good for stomach, liver and heart'.

Medicinally, cloves are still represented in the *British Pharmacopœia* (as clove oil) and in the *British Pharmaceutical Codex* (as clove and clove oil). The *Codex* has little to say of the uses of clove except that it is 'a carminative and infusions have been used as vehicles for mixtures'. It is a little more expansive about clove oil which is described as 'a carminative and may be administered on sugar. Applied externally, it is rubefacient, counter-irritant and slightly analgesic'. Probably its main use, however, is in dentistry as a temporary soother of pain. Of its many non-medicinal uses, the flavouring of drinks, alcoholic and non-alcoholic, is one of the most important. It is the major flavour of the Italian Rosoglio liqueur, and it is also included in cherry and plum 'brandies'. Spiced ales and beers nearly always contain cloves and its culinary uses are widespread. These are but a few of the modern uses of 'the fragrant clove'. It may well disappear in time from our pharmacopœias but it will long linger on in our midst as one of that select group of spices which have played such a persistent role in the affairs of mankind.

Stomach Stones

It has long been known that the stomachs of crocodiles contain a quantity of stones. Hitherto the assumption has been that these subserve a digestive function, helping to grind up hard structures such as bones. According to Dr. H. B. Cott, of the University Museum of Zoology, Cambridge, however, this is not the case. In a fascinating article on 'The life of the Nile crocodile', in the autumn edition of *The Times Science Review*, he gives his reasons for the view that these stones act as ballast and 'subserve hydrostatic function'.

It has been found that the stomachs of young crocodiles in their first years of life never contain stones, whereas those of adults invariably do so. The age at which stones are first found in the stomach varies with the conditions under which crocodiles live. Thus, those in waters with a stony bottom, such as Lake Albert, acquire them before attaining a length of 1.25 metres, whereas those in rivers with bottoms of sand or mud, such as the upper Zambesi, do not acquire them until they reach 2 metres in length. Apparently crocodiles living over a bottom of ooze or sand will travel quite long distances to find their gastroliths. One of the many arguments in favour

of these stones subserving a hydrostatic function is that, no matter what the age or size of the crocodile, it tends to carry a standard load of stones, which is equivalent to about 1 per cent. of the body weight. A further argument in favour of this hypothesis is that when a crocodile is submerged, buoyancy reduces its weight by just over 90 per cent. This means that a crocodile weighing 91 kg. will weigh 7 kg. when submerged, but it will also carry about 1 kg. of stones. This additional ballast has two advantages for the crocodile: it allows him to lie on a river bottom without being dragged by the current, and it helps him in his struggles when drowning large prey such as waterbuck. Yet a third argument in favour of the hydrostatic theory is the instability of stoneless young crocodiles when placed in deep water, compared with 'the easy poise of their stone-bearing elders'.

Lincoln and His Nurses

'OUR hospitals are so bad men fight against being sent to them'. So wrote a soldier of the conditions in the American Civil War and it is clear from an account in the *New York State Journal of Medicine* (1961, 61, 1944) that nursing and hospital conditions in this war were quite as bad as those in the Crimean War. Until the Civil War the army had no general hospital. Nursing throughout the country, of course, was of an appallingly low standard. In municipal hospitals, such as Bellevue in New York, some of the nursing care was provided by prostitutes who, when arrested, were given the option of going to prison or to hospital service for ten days.

When war actually broke out and the appalling condition of the sick and wounded was appreciated, the ladies rose nobly to the occasion, but their lot was anything but an easy one. One, for instance, reported that 'hardly a surgeon of whom I can think received or treated them with even common courtesy'. General Sherman's attitude perhaps was typical of the reaction to nurses: 'Send always a barrel of pork instead of a woman'. Even the interest of those enthusiastically supporting the ladies in their attempts to provide nurses was not necessarily altruistic. The Hon. Henry Raymond of *The New York Times*, it is said, 'organized a band of ladies to go to Washington to serve in the hospitals. The nobility of Mr. Raymond's motives is open to question since he was subsequently accused of having a cosy little romance with the woman he put in charge of the contingents of potential Florence Nightingales'. Of the many stories told of these days one illustrates well the conditions under which these volunteer nurses had to work. On a hospital transport a nurse decided that 'three men to a tin wash basin was enough, or four "if they didn't wash too hard" '. An old corporal, however, thought otherwise. 'Stop, Marm', he said as he found her about to empty the basin, 'that water will do for several of us yet. Bless you! I make my coffee of worse than that'. Whatever others may have thought, however, they were appreciated by Lincoln: 'They say these are the days that try men's souls; they try women's souls as well and when this war is ended I will never forget the noble women of the north'.

ADVANCES IN MEDICINE

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EVEN the compass of this whole Special Number could not contain all that could be written on the advances in this field of medicine, and only a few examples can be included in this opening article. The choice of the five subjects which are discussed has been based on their potential value but relative difficulty in use, and by the seriousness of the conditions which they are designed to relieve.

THE DRUG TREATMENT OF HYPERTENSION

The drug treatment of hypertension is fraught with controversy which has not by any means disappeared with the introduction of drugs which solely block adrenergic fibres. There are still those who believe, with Kitchin and his colleagues (1961), that 'drugs with a selective action on the sympathetic nervous system are not yet established as the best method of lowering the blood pressure, and interest in new ganglion-blocking agents continues'. The advantage to patients, however, of drugs which do not block the autonomic ganglia and which produce their hypotensive effects solely by their action on adrenergic fibres is sufficiently great to justify a careful examination of the claims made for them.

Bretylium tosylate is being largely replaced by guanethidine sulphate, as the action of the former is sometimes irregular, and tolerance to the drug rapidly develops in a high proportion of patients (Evanson and Sears, 1960). Guanethidine, on the other hand, acts with reasonable regularity, and the development of tolerance does not seem to present a major problem.

Dollery and his colleagues (1960) have made a careful clinical and pharmacological study of this drug. They have shown that absorption from the gut is incomplete, and that when guanethidine is given by mouth or intravenously it is slowly excreted in the urine, not only as the unchanged drug, but also as three closely related metabolites; excretion in the fæces is also prolonged. In their rat experiments they showed that the concentration of the drug is largely intracellular, being highest in the kidney.

Their therapeutic results showed good control (i.e. a standing blood pressure of 160/100 mm. Hg or under on most occasions) in 42.5 per cent., and a fair control (i.e. at least 20 mm. Hg reduction in diastolic blood pressure) in another 42.5 per cent. of patients. Thus, 85 per cent. of their 80 patients described as having very severe hypertensive disease had good or fair control over a period of nine months. These results, obtained by a single daily dose, are satisfactory, and were achieved without the addition of drugs of the chlorothiazide type, which are usually unnecessary, although, as would be expected, they do enhance the effect of guanethidine.

Like those of Leishman and his colleagues (1961) (71 per cent. with good control), they compare not unfavourably with the results obtained with ganglion-blocking agents such as pentolinium, mecamylamine or pempidine

tartrate, without the patient having to pay the cost of intractable constipation, dry mouth, visual disturbances and difficulty in micturition. Incidents of postural hypotension are also less frequent. There are, however, reactions which must be recognized and some of these are troublesome, but can be minimized by increasing the dosage slowly and keeping it as low as possible.

Patients treated with guanethidine, like those given ganglion-blockers, get their greatest fall in blood pressure when they are standing, and this is particularly so on getting up in the morning. Four of Dollery's 80 patients were so severely affected by the early morning postural hypotension that less than 'fair control' had to be accepted for them. Troublesome postural hypotension, however, is not often encountered. As in the case of those who are treated with bretylium tosylate, some patients suffer from hypotension on exercise, and this can be severe enough to result in actual fainting. This is particularly the case early in the day, and in those patients who have early morning postural hypotension. Taylor and Donald (1960) found that the fall in blood pressure on exercise was less with guanethidine than with bretylium, and that guanethidine, unlike bretylium, did not result in increased pulmonary vascular resistance in hypertensive subjects. Nevertheless, exercise hypotension can be a troublesome consequence of guanethidine therapy.

Although side-effects are quite common, less than one-third of Dollery's patients had more than minor discomfort. Coarse muscle tremor occurred in some, and was severe enough in two patients to cause the treatment to fail. Looseness of the stools, or actual diarrhœa was more frequent, particularly in the mornings, requiring in some instances kaolin mixture, codeine phosphate (32 mg.), or pempidine (2.5 mg. twice daily) for its control. Leishman and his colleagues (1961) reported frequent complaints of muscle aching and weakness, particularly during exercise, in their patients. The occurrence of bradycardia makes for caution when digitalis is being used in patients who are taking guanethidine. Fluid retention with œdema, the cause of which is still unexplained but which nevertheless responds to diuretics, also occurs, and some of these patients get a temporary loss of blood-pressure control which is distinct from drug tolerance (Leishman *et al.*, 1961). As in any patient with hypertension, the achievement of a satisfactory lowering of blood pressure may be followed by weariness and weakness, but fortunately this is usually temporary. In addition, guanethidine can cause severe depression, which disappears when the drug is withdrawn.

There are other complications, but the sum total of these undesirable effects is far more endurable than those from the ganglion-blocking agents, and in practice they do not often incommode patients to any great extent.

It is not suggested that guanethidine provides a complete or even a particularly good answer to the problem of the treatment of hypertension, but its introduction has been a real advance and the passage of time has so far enhanced rather than reduced its reputation. It could, however, be argued that mecamylamine is still the drug of choice for patients with

malignant hypertension, at any rate until satisfactory reduction in the blood pressure has been achieved, as it has a greater flexibility in exercising its control. Guanethidine can be substituted at a later date when a satisfactory hypotensive effect has been achieved if the patient's life is rendered miserable by the results of ganglion blockade.

WHICH HYPERTENSIVE PATIENTS SHOULD BE TREATED?

It is not entirely illogical to have discussed which drug is at present most widely used for the control of hypertension before discussing whether a given hypertensive patient should be treated by drugs at all, as it is largely on the effectiveness and simplicity in use of these drugs that the decision depends as to whether or not they should be used in milder instances.

There is no question about the necessity for using them in retinal grade IV hypertension: i.e. with retinal hæmorrhages and exudates and with papillœdema. The outlook in this state has been changed from an expectation of life of a few months or about two years from the time of diagnosis to 45 per cent. survival at three years and 30 per cent. at six years in patients in whom the blood urea was under 60 mg. per 100 ml. at the beginning of treatment (Harington *et al.*, 1959). Smirk (Hodge *et al.*, 1961) has recently published his figures for an eight-year period, during which patients were treated with various hypotensive agents, mostly ganglion-blockers. The results show an improvement in mortality in retinal grade III hypertension, i.e. retinal hæmorrhages and exudates without papillœdema, as well as in grade IV patients. In retinal grade II patients, i.e. with only retinal arterial disease, substantial improvement was obtained, and loss of life during the eight-year period was nearly three times as great in the grade II control patients as in those who were treated.

Most practitioners will wish to treat patients with grade IV and grade III retinopathy, and men with diastolic pressures persistently over 120 mm. Hg, or women before the menopause with a diastolic pressure constantly more than 130 mm. Hg. After the menopause the ill effects of hypertension are more equal in the sexes. Many will also treat patients of both sexes with grade II retinopathy, who have hypertensive heart disease, and some with the less severe manifestations of renal impairment. The question of treating the less severely affected patient is still an open one and depends largely on the simplicity and efficacy of the hypotensive agents which are available. If it is once decided to treat a patient with hypotensive agents, thorough supervision is required. This means the frequent determination of the blood pressure throughout a 24-hour period at spaced intervals, if adequate control is to be maintained, and adequate control means a close approximation to a normal pressure. This necessitates determination on the part of the patient as well as the doctor.

The whole question of the treatment of hypertension has been recently and admirably reviewed by Pickering and his collaborators (1961). They do not confine themselves to drug therapy alone, and preface the detailed con-

sideration of methods by a discussion of the nature of hypertension and the assessment of its treatment.

PROPHYLACTIC ANTICOAGULANTS IN VENOUS THROMBOSIS

The introduction of anticoagulants into the treatment of venous thromboses of the lower limbs nearly two decades ago was a notable therapeutic advance, producing a fall in mortality from pulmonary embolism from around 15 to 20 per cent. to about 1 per cent. or under in patients in whom there were clinical manifestations of thrombosis in the lower limbs.

Recently it has been realized that anticoagulants can also be used most rewardingly as a prophylactic in suitable circumstances. An excellent control study was reported by Sevitt and Gallagher (1959) from the Birmingham Accident Hospital. They established the important fact that two-thirds of patients who have deep-vein thrombosis proven by careful dissection at necropsy have no clinical evidence of such thrombosis during life. These patients had not complained of either pain or swelling of the legs. There had been no tenderness along the line of the veins and no pain on compression of the muscles laterally or on extension of the ankle-joint. This finding accounts for the high incidence of fatal pulmonary embolism which occurs without any previous suspicion being entertained that there were deep-vein thromboses in the legs. It also accounts for the unhappy circumstance when a superficial venous thrombosis has been regarded as safe, only for the patient to develop a pulmonary embolus, the explanation being that the superficial thrombosis had spread to the deep veins without any evidence being manifest clinically. Further, it explains what has been widely realized for years, namely, that the danger of embolization lies in the 'good' leg and not from the leg swollen as a result of deep thrombosis. Sevitt and Gallagher took as their material patients with fractures of the neck of the femur and their results were striking. Embolism did not occur in any patient treated with phenindione, whereas in the control series there was an embolism in 18 per cent. of cases, and in 10 per cent. the embolism was fatal. Venous thromboses were detected clinically in 28.7 per cent. of patients in the control series, whereas it was found in only 2.7 per cent. of those who were under treatment with anticoagulants. The post-mortem findings were just as impressive. Evidence of thrombosis was found in 83 per cent. of the 35 control cases in which the leg veins were carefully dissected, compared with only 14 per cent. of the 21 cases in the anticoagulant series.

Similar results have been reported by Turnbull (1960) in patients following gynæcological surgery. Both he and the Birmingham workers found that the incidence of hæmorrhage following operation was higher in the treated series than in the control, but in neither was it of any serious moment.

As a result of this work it is reasonable to consider using prophylactic anticoagulants in obese patients over the age of 45, who are immobilized in bed for more than a few days, as these factors seem to predispose towards pulmonary embolization.

Anticoagulation is only one method of prophylaxis; another of real practical importance is to raise the limb to 15 degrees above the horizontal, as this increases the rate of venous flow, reducing the clearance time of injected radio-opaque material to between one-third and one-fifth (McLachlin *et al.*, 1960).

PROPHYLACTIC ANTICOAGULANTS IN CORONARY THROMBOSIS

As a result of careful work on both sides of the Atlantic, it is generally accepted by most physicians that anticoagulants have established themselves in the treatment of acute myocardial infarction. As yet, however, there is no direct evidence that anticoagulants prevent further thrombosis or the beginning of thromboses in arteries, such as the coronary arteries, and it is possible that the reduction in mortality is achieved by the effect of the anticoagulants on the venous side of the vascular system. The number of thrombo-embolic incidents is reduced by about half, as is the chance of an immediately fatal pulmonary embolism or the development of a slower but fatal outcome as a result of extra strain being thrown on a damaged heart by extensive or repeated infarction of the lung.

The position is far less clear and more controversial when we come to consider prophylaxis and the value of long-term anticoagulation in preventing a recurrence and prolonging life in patients who have had an acute myocardial infarction. The importance of obtaining a clear answer is obvious, as prolonged anticoagulation not only involves the patient in a certain amount of trouble and risk, but also, if its use were universally accepted and practised, would present the pathological services of the country with enormous administrative problems. An example is the belief by some pathologists (Biggs, 1960) that the relatively simple method of estimating the plasma prothrombin activity by a one-stage prothrombin time is not sufficiently constant and accurate for reliance to be placed upon it when single readings are taken from a given patient at relatively widely spaced intervals in time.

The conclusions drawn by the Medical Research Council Anticoagulant Working Party (1959) from their preliminary analysis were tentative and largely inconclusive in that, although the mortality rate in the first six months after recovery from the acute attack was less in the treated than in the control group, the difference was not statistically significant. There was no difference in mortality at the end of two years, but there was a significant reduction in the rate of re-infarction in the first six months. These are modest claims, but even they have been searchingly questioned by McMichael and Parry (1960), who point out the difficulty of assessing anything other than the clearest-cut differences in this condition. The prognosis varies so widely with the age of the patient, the presence of hypertension and of heart failure, that minor differences in a control and treated series could lead to an apparently more diverse result than is in fact the case. The survival rate is at any rate high—about 66 per cent. for the

first five years—and is higher in certain classes of person, notably in doctors.

McMichael also made the point that if there is a therapeutic action and the drug prevents arterial thrombosis, it is curious that it should only act for six months. Detailed scrutiny of his article and of the report by the Medical Research Council committee leads most clinicians no further than to a determination to judge the individual case entirely on its merits.

There is little precise evidence as to the value of anticoagulants in the treatment of patients with angina pectoris, but Owren (1961) includes angina pectoris of less than two years' duration among his five groups of patients for whom he recommends prolonged anticoagulation.

It is unfortunate that there is no more precise information about the value of anticoagulants in the syndrome of acute coronary insufficiency, as in this condition anticoagulants might well have a special place. Acute coronary insufficiency is deemed to be present when anginal pain is of increasing severity, frequency and duration, suggesting not infrequently myocardial infarction, but unaccompanied by the typical electrocardiographic or biochemical changes of muscle damage. It has been estimated that between 25 and 30 per cent. of these patients develop frank infarction within a month of the onset of these symptoms, and the finding that only 6 per cent. did so in a series of 318 treated with anticoagulants by Nichol and his colleagues (1959) is encouraging. Similar encouragement comes from Wood's recent report (1961) on 100 treated patients.

PROPHYLACTIC ANTICOAGULANTS IN PERIPHERAL ARTERIAL THROMBOSIS

When we turn to the treatment of peripheral vascular disease with anticoagulants, there is an increasing number of reports. In a recent study of a large series of patients with femoro-popliteal and aorto-iliac thrombosis, Singer and Rob (1960) found that no benefit resulted to their patients with claudication, or with a limb threatened with gangrene, from the prolonged use of anticoagulants. Long-term therapy, however, has been recommended following endarterectomy, and 10 patients with thrombo-angiitis obliterans have been treated with phenindione for a mean of five years without amputation being required (Smith, 1960).

PROPHYLACTIC ANTICOAGULANTS IN CEREBROVASCULAR DISEASE

Disease of the peripheral arteries affecting the brain constitutes a problem of its own. From first principles one might expect improvement in the presence of a cerebral thrombosis, and harm if the patient is suffering from a cerebral hæmorrhage. The difficulty is that some of the most experienced of observers claim to be quite unable to decide whether a hæmorrhage or a thrombosis is the cause of the patient's clinical state. A study of anticoagulant treatment of an acute stroke has been carried out, and the results showed that those who were treated did less well than those

who were not. In fact, as soon as an answer appeared the study was discontinued as it was considered to be dangerous (Shaw, 1960).

A controlled clinical trial of long-term anticoagulant therapy in cerebrovascular disease has recently been reported by Bradford Hill and his colleagues (1960).

> The incidence of further cerebrovascular accidents did not differ significantly in the treated when compared with the untreated group of patients. There were, however, four deaths from cerebral hæmorrhage and one from hæmopericardium in the treated group, whilst there were none from hæmorrhage in the untreated group.

The authors' conclusion was that anticoagulant therapy had no place in the general treatment of cerebrovascular disease except in certain restricted types, and might carry a special hazard from hæmorrhage.

Barham Carter (1960), however, believes that in ingravescent cerebral infarction, when cerebral infarction is of gradual onset, and the neurological lesions are incomplete after two or more hours, anticoagulants are indicated, and in his hands their use has not proved alarming. He feels that this treatment is comparatively safe provided patients with severe hypertension or with loss of consciousness are excluded.

THE NEW PENICILLINS

The big advances in the control of infection which could follow on the isolation at the Beecham Research Laboratory of the 'nucleus' of penicillin, 6-amino-penicillanic acid (Batchelor *et al.*, 1959), depend not only upon the skill of the research worker, but also on the wisdom and restraint of the clinician in using the new preparations which are presented to him.

Information has rapidly become available about the properties and clinical effects of the first products resulting from this research: namely, methicillin and phenethicillin. The prime importance of methicillin is that it is not destroyed by staphylococcal penicillinase as are benzylpenicillin and phenoxymethylpenicillin, and thus the production of resistance to it by the usual mechanism of inactivation by penicillinase does not occur. Methicillin is destroyed by the acid in the stomach and has to be given by intramuscular injection every four to six hours. The frequency of the injections is determined by the rapidity with which it is absorbed and excreted, by the size of the dose which is a large one, and by the relative weakness of activity of methicillin, which is about 1/100th of that of benzylpenicillin.

Successful clinical trials have been reported by Douthwaite and Trafford (1960), Stewart and his colleagues (1960), Elek and Fleming (1960), and Douthwaite and his colleagues (1961), and their clinical observations support the bacteriological studies of Rolinson and his colleagues (1960), and the chemotherapeutic studies on animals by Brown and Acred (1960). Rolinson and his co-workers showed that methicillin was stable to staphylococcal penicillinase, and was active against penicillin-resistant staphylococci. Brown and Acred (1960) found that the same preparation was highly effective against staphylococci which were resistant to benzylpenicillin,

confirming *in vivo* the experiments done *in vitro*. They also showed that methicillin was remarkably free from toxic actions, and this appears to be true also in man as injections cause no more local pain than does benzylpenicillin, and apparently there is no greater tendency for hypersensitivity reactions to be produced. Although there is no report of any failure therapeutically due to the development of methicillin-resistant staphylococci in patients, naturally resistant strains have already been reported from laboratory studies, and cultures of *Staphylococcus pyogenes* have been 'trained' artificially to high levels of resistance (Jevons, 1961; Rolinson, 1961; Knox, 1961). Fairbrother and Taylor (1961) have demonstrated increasing resistance *in vitro* after successive subcultures in increasing concentrations of methicillin. Both Rolinson and Knox stressed the rarity of the resistance rather than its frequency as the remarkable feature, but nevertheless the demonstration of a few strains is a warning that this potentially most valuable penicillin should be restricted in its use to severe infections with coagulase-positive resistant staphylococci, and that every effort should be made to prevent cross-infection from patients so treated.

Another preparation which has resulted from the isolation of 6-aminopenicillanic acid with the addition of a new side chain is phenethicillin. It is not destroyed by the acid in the stomach and is well absorbed when given orally. Garrod (1960a) reported that it was more active than benzylpenicillin against penicillinase-producing strains of *Staphylococcus aureus*, and was also more active than phenoxymethylpenicillin, although here the difference was less than between phenethicillin and benzylpenicillin. Fairbrother and Taylor (1960) confirmed that it was rapidly absorbed and thought it should prove a useful oral product.

In an article, whose value is only rivalled by its brevity, Garrod (1960b) has compared *in vitro* the relative activity of the four different penicillins now in clinical use against various organisms, including the *Staphylococcus aureus*. Methicillin he put in a class apart in the treatment of serious infections with resistant staphylococci. If, however, the infection is less severe, he suggested that phenethicillin, with its acid-resisting property enabling it to be given by mouth, is more slowly inactivated than phenoxymethylpenicillin, the other oral penicillin, and much more slowly than benzylpenicillin. For all organisms other than the staphylococcus, with the exception of two uncommon species of proteus, benzylpenicillin exceeds all other penicillins in activity. He also found that phenoxymethylpenicillin is the nearest in activity to benzylpenicillin against hæmolytic streptococci and pneumococci, and therefore still the oral penicillin of choice in infections with these organisms. He once more emphasized the point that results obtained in *in vitro* experiments are not always accurately reflected in bedside therapeutics. They are, however, generally useful, and it seems from his work, as from others, that the penicillin of choice, for the treatment of infections with resistant staphylococci, whose resistance is the result of the production of penicillinase, is methicillin, whilst against other organisms

benzylpenicillin far exceeds in activity all other penicillins. Fairbrother and Taylor (1961) also hold the opinion that methicillin should be reserved for severe staphylococcal infections caused by organisms resistant to the usual antibiotics.

It thus appears that at the present time, apart from the really severe infections with resistant organisms for which methicillin is required, less severe staphylococcal infections should continue to be treated, after sensitivities have been established, with either erythromycin, novobiocin, oleandomycin or vancomycin, or a combination of two of these. Phenoxymethylpenicillin is still the most active oral penicillin against streptococci and pneumococci but, if oral penicillin is to be used in mild staphylococcal infections, phenethicillin is to be preferred.

The search for new synthetic penicillins continues, and experience is now being gained with α-phenoxypropylpenicillin, at present called P.A.248, which is active in the presence of staphylococcus penicillinase. It can be given by mouth, and Nagley (1961) has treated five patients with pneumonia, with penicillin-resistant staphylococci in the sputum, with success. Williamson and his colleagues (1961) have shown that high levels of concentration in the serum can be obtained by oral administration of P.A.248, and from these levels have concluded that it is likely to be the most effective of the three oral penicillins—phenoxymethylpenicillin, phenethicillin and P.A.248—against resistant staphylococci and in streptococcal infections.

More recent still are reports about a new penicillin, 'penbritin' (6[D(−)α-amino-phenylacetamido] penicillanic acid), (Rolinson and Stevens, 1961; Brown and Acred, 1961; Knudsen *et al.*, 1961; and Stewart *et al.*, 1961). This penicillin is bactericidal with very low toxicity and incidence of side-effects, and can be given by mouth as it is acid resistant. Its activity is somewhat less than that of benzylpenicillin against staphylococci, streptococci and pneumococci, and it is affected by penicillinase. Its really exciting properties are its effects against gram-negative bacteria such as *E. Coli*, the salmonellæ and the *Hæmophilus influenzæ*.

The responsibility of the clinician for the proper use of these new penicillins, so that the development of resistant strains of staphylococci may be kept to a minimum, cannot be exaggerated. Success in this will depend on careful assessment of all the clinical circumstances, supported whenever possible by the expert help of a bacteriologist.

THE TREATMENT OF ACUTE RESPIRATORY FAILURE

The treatment of acute respiratory failure demands an increase in the supply of oxygen while maintaining adequate ventilation. The difficulties and dangers of combating hypoxia with oxygen have been realized for some time. The sight of a deeply cyanosed patient entering unconsciousness as his colour becomes a healthy pink, only to return to consciousness and cyanosis when the oxygen supply is stopped, is a common experience. This is due to depression of ventilation consequent upon the giving of oxygen. A serious

component in the production of respiratory failure is often blockage of the airways by secretions which are not properly cleared by suction.

The whole situation can be combated, with sometimes striking success, by the use of a tracheotomy through which is inserted a tube surrounded by an inflatable cuff. Oxygen can be given via the tube, while a constant minute ventilation is maintained by an intermittent positive/negative pressure respirator. Secretions from the bronchial tree can be efficiently sucked through the tube. Artificial respiration is often required in these patients for one to two weeks, and their management clearly requires expert nursing, clinical and biochemical skills. It also involves mechanical problems as maintenance of the respirator is of first importance. It is therefore a measure that cannot be undertaken lightly and it may necessitate moving the patient to a bigger centre. This involves a serious decision, and thus any information, such as that given by Munck and his colleagues (1961), as to when it should be considered, is welcome. Munck treated in this manner 23 consecutive patients with diffuse chronic lung disease whose lives were threatened by acute respiratory failure. Fifteen of the patients lived and eight died. The striking point which came out of the analysis of their results was that the patients who recovered were those who were still able to work before the onset of respiratory failure, and that the history rather than the immediate clinical picture or biochemical state determined the life expectancy. The conclusion reached was that when no pulmonary reserve is present the results of this complicated treatment were hardly better than with ordinary conservative treatment.

Conservative methods have recently been improved by the application to patients with acute respiratory failure of the principles enunciated by Kellaway (1959) for the treatment of acute anoxic cardiac failure in pulmonary heart disease. His aim was to keep patients on continuous and adequate oxygen therapy in a tent, so that their oxygen saturation was maintained above 85 per cent., and CO_2 narcosis avoided. This cannot be satisfactorily achieved either by giving continuous oxygen slowly or by intermittent administration but, when respiratory stimulants were combined with oxygen given continuously and at an adequate rate, Kellaway reported levels of oxygen saturation of 90 per cent. or over after the first twenty-four hours of treatment.

His method was to give 5 ml. of nikethamide intramuscularly every four hours for seventy-two hours, and then attempt to reduce the frequency. If the patient showed signs of CO_2 narcosis before the treatment was begun, more vigorous use of respiratory stimulants was required: 30 mg. of amiphenazole were given at one hour, and 5 ml. of nikethamide at the next hour; thus the two stimulants were given at alternate hours, or two-hourly for the individual drug. The value of amiphenazole, however, seemed doubtful. If, in spite of this degree of stimulation of the respiratory centre, oxygen produced CO_2 narcosis, nikethamide was given in 4-ml. doses intravenously at intervals of not less than half-an-hour. The rate of withdrawal

of oxygen therapy and the respiratory stimulants depends on the presence of cyanosis and its rate of reappearance.

This regime is naturally accompanied by antibiotics to combat infection, suction to remove secretions and the careful use of sedatives. Kellaway used pethidine, with levallorphan, 2 mg. for every 100 mg. of pethidine, given if respiratory depression was present, and found this satisfactory. It is of interest that Kellaway found this treatment reduced the mortality in his patients during the first four days, but had less effect afterwards, when the extent of the chronic disease process in leading to the patient's acute anoxic cardiac failure determined the prognosis. This treatment was designed for patients with acute anoxic cardiac failure from pulmonary heart disease, but Kellaway points out how easy it is for the clinician to miss this kind of heart failure when severe pulmonary infection is present, and it may well be that some patients who respond to it are suffering from both acute respiratory failure and acute anoxic cardiac failure. It is practicable in the smaller hospitals which have no facilities for maintaining a mechanical respirator, and when thus used can on occasions result in recovery from apparently hopeless situations.

THE TREATMENT OF ACUTE RENAL FAILURE

The considerable experience gained in different centres in the use of the artificial kidney has been admirably reviewed by Jackson (1960), Milne (1960) and Ross (1961), and their colleagues.

Before turning to their examination the present position of the treatment of acute renal failure without hæmodialysis will be briefly considered. This has not changed radically in the past year, but there has been a shift of emphasis towards the extreme importance of avoiding infections in these patients by isolation, prophylactic antibiotics and avoidance of the intravenous route of administration. A diet composed solely of carbohydrate is given as it is believed that it reduces protein breakdown to a minimum. Vitamins and 100 g. of lactose in 100 ml. of water are given by mouth daily, with additional water to replace fluid loss in the urine, the vomit, the stools or from excessive sweating. Only sensible fluid loss is replaced, and no more than a total of 600 ml. of fluid should be given in twenty-four hours.

In patients who cannot take fluids by mouth—these are chiefly surgical cases as opposed to medical or obstetrical ones—sterile 40 per cent. lactose will have to be given by catheter into the superior vena cava. If lactose of this strength—and this strength is required in order to prevent loading the patient with more than the minimum amount of fluid—is put into a vein smaller than the superior vena cava, it will cause thrombosis. Intravenous infusions, however, do carry a grave risk of introducing a blood-stream infection, and positive cultures from the blood or from the tip of the catheter are common (Milne *et al.*, 1960). Here is a reason why a change in emphasis has occurred as it has been realized that infection is a very grave risk indeed in these patients, and that intravenous infusion should be avoided so far as

possible. These patients should also be treated in isolation and protected from cross-infection by every available means.

Frequent observations of the electrolyte state, as well as the degree of nitrogen retention, will be required, especially when diuresis begins. A high plasma potassium, i.e. above 7 mEq. per litre, is often an indication for hæmodialysis. An attempt should be made, however, to reduce it by the use of oral ion-exchange resins of approximately 45 g. daily, or, if this is not possible, up to 200 g. a day rectally as sodium polystyrene sulphonate (Jackson *et al.*, 1960).

The electrolyte changes are particularly important in patients who have been subjected to widespread trauma with much muscle damage. Such patients do badly, and in them excessive catabolism occurs at once from the early stages, with a special tendency to a rapid and dangerous development of hyperkalæmia. The excessive catabolism in uræmia from trauma is possibly the reason why drugs believed to have anti-catabolic effects, such as testosterone, progesterone and, recently, norethandrolone, are relatively ineffective in these patients as compared with those in whom acute renal failure is from obstetrical or, to a lesser extent, medical causes: e.g. acute nephritis. Obstetrical cases are usually the result of concealed accidental hæmorrhage in the later stages of pregnancy, and may show little sign of recovery of renal function for three weeks. It is during this supportive period that Blagg and Parsons (1960) believe that norethandrolone is of special value and may even obviate the use of the artificial kidney in some instances; they also found it effective in acute renal failure in pregnancy due to other causes: namely, after hæmorrhage from a placenta prævia or an abortion. Part of the effect of norethandrolone may be the combating of the negative nitrogen balance which occurs normally for at least ten days after parturition (Venning *et al.*, 1959). Blagg and Parsons believe that norethandrolone is more effective and quicker in action than methyltestosterone or progesterone, and found that it reduced the average amount of protein breakdown by about 70 per cent. They recommend 30 mg. of norethandrolone by mouth, or 50 mg. by intramuscular injection, daily, and have noted an effect within the first twenty-four hours, but they are not as yet able to determine the optimum period of treatment. The number of patients who were treated was small, and further reports must be awaited before the use of norethandrolone can be generally accepted as a reason for postponement of admission of these obstetrical cases to a special centre where hæmodialysis is available.

THE ARTIFICIAL KIDNEY

The clinical state of the patient is the most important factor in determining whether or not dialysis should take place. This is clearly a matter of judgment. If the best results are to be obtained, admission to a special centre should be sought before the patient becomes drowsy and twitching, with uncontrollable vomiting. Evidence of deterioration therefore in the direction of this clinical picture should lead to the patient's transfer, especially if the

blood urea is rising to the region of 400 mg. per cent. It is also agreed by most experts that a plasma bicarbonate of less than 12 mEq. per litre, and/or a plasma potassium of greater than 7 mEq. per litre, despite therapy with cation-exchange resins, should lead to admission to a special centre unless the clinician can be quite certain that the cause of the acute renal failure is due to other than kidney damage. Acute renal circulatory failure, sometimes termed pre-renal azotæmia, can occur in diabetic coma, or with a hæmatemesis, and in surgical patients on continuous aspiration of the intestinal contents. Here the management is to supply the missing electrolytes.

The results of hæmodialysis depend, of course, on the type of case in which it is employed. In certain patients with acute glomerulonephritis the results can be good if dialysis is undertaken sufficiently early. Children, however, seem to do less well than adults. The same good results can be gained with the renal lesion of Henoch-Schönlein's purpura, and in acute renal failure supervening on chronic in, for instance, patients with polycystic kidneys. If acute tubular necrosis is due to medical conditions, e.g. poisoning, notably with barbiturates, salicylates or mercury, or to obstetrical ones, 75 to 80 per cent. of patients will recover. If, however, in addition they have hepatic lesions, most patients will die from them. Patients with acute tubular necrosis due to surgical conditions or severe trauma do less well, the average survival rate being only 25 to 40 per cent.

Jackson's conclusion as a result of his extensive experience is: 'All patients with more than a transient acute renal failure should be transferred to specialized units', and there can be little doubt about the wisdom of this advice provided one is suitably placed geographically.

CHRONIC RENAL FAILURE

Chronic pyelonephritis.—The recognition of chronic pyelonephritis as a cause of chronic renal failure, is a big advance in our understanding, and already methods are being devised to enable the diagnosis to be made in as early stages as possible. The treatment of such patients with a series of preparations taken in rotation for a week or ten days at a time may prove helpful in destroying organisms in the kidney parenchyma and thus prevent further renal destruction and scarring. Tetracycline in doses of 250 mg. twice daily, mandelamine 0.25 g. four times daily, sulphadimidine 1 g. thrice daily, and nitrofurantoin 100 mg. twice daily, are suitable preparations for use in rotation. It must be stressed, however, that there is no controlled series to show that this really works, and some of the drugs are not without potential danger. The decision to use them is thus a matter for judgment in each case.

Hypertension.—Wilson (1960) has reported the extension of his previously reported work (Wilson and Abrahams, 1957), and the effects of hypotensive therapy on renal function in patients with hypertension and renal disease. In the early stages there was usually no significant change in renal function, and some patients were relieved of their hypertensive symptoms without

further increase in blood urea. When these observations were continued over a period of six months to four years on hypotensive therapy, it was found that in chronic type I nephritis renal function remained unchanged or actually improved except in those with a blood urea initially over 60 mg. per 100 ml., but in type II nephritis, or type I with a high initial blood urea, although the hypertensive symptoms might be relieved, the blood urea showed a progressive rise. As Wilson points out, however, such a rise might well have occurred in the absence of treatment, and in certain patients even with an initial blood urea of 100 mg. per cent., no further rise occurred although the blood pressure fell with hypotensive drugs. He concluded that the effect on renal function is related intimately to the original disease and the renal function at the onset of treatment, and suggested that in chronic type I nephritis with no more than slight renal impairment, relief of symptoms and delay in the onset of uræmia may result from hypotensive therapy. In the same way, other forms of slowly progressive renal disease, such as chronic pyelonephritis, may be benefited.

Hæmodialysis.—As has been stressed, this is especially useful in acute renal failure, usually from tubular necrosis, but it can be useful in certain instances of acute renal failure occurring in a patient with chronic renal disease. Polycystic disease of the kidneys, in which chronic renal failure can persist for years before a fatal outcome, is an example of this. The practicability of repeated hæmodialysis has been increased by the introduction of indwelling cannulæ made of inert polytetrafluorethylene (P.T.F.E.) into an artery and a vein. The cannulæ are connected in such a way that an arteriovenous fistula is formed and thus they are kept patent between dialyses (Scribner *et al.*, 1960; Chisholm, 1961).

Homotransplantation.—Successful homotransplantation of a kidney between identical twins has been reported from Montreal (Dossetor *et al.*, 1960), and from Edinburgh (Woodruff *et al.*, 1961). Dossetor's patient, who has been followed up for more than a year, had chronic bilateral pyelonephritis, and a kidney from a healthy twin sister was grafted, with subsequent removal of her own diseased kidneys. The patient remains well, with normal renal function and a normal blood pressure.

Merrill and his colleagues at Boston (Murray *et al.*, 1958) have reported eight such cases, and recently one between non-identical twins (1960). Before operation a very close antigenic relationship was demonstrated between the twins and the transplantation was undertaken after all-body irradiation in low dosage, the idea being to inhibit the production of autoantibodies resulting from the transplant. The patient was in good health more than a year after operation despite the fact that before it he had been suffering from chronic glomerulonephritis with uræmia. Renal biopsy of the transplant, however, has shown changes suggesting that it was undergoing very slow rejection. At present therefore successful transplantation can only be expected between identical twins.

References

Batchelor, F. R., *et al.* (1959): *Nature (Lond.)*, **183**, 257.
Biggs, R. (1960): 'The Pathogenesis and Treatment of Occlusive Arterial Disease', London.
Blagg, C. R., and Parsons, F. M. (1960): *Lancet*, **ii**, 577.
Brown, D. M., and Acred, P. (1960): *Ibid.*, **ii**, 568.
——, —— (1961): *Brit. med. J.*, **ii**, 197.
Carter, A. Barham (1960): *Quart. J. Med.*, **29**, 611.
Chisholm, G. D. (1961): *Brit. med. J.*, **ii**, 30.
Dollery, C. T., Emslie-Smith, D., and Milne, M. D. (1960): *Lancet*, **ii**, 381.
Dossetor, J. B., *et al.* (1960): *Ibid.*, **ii**, 572.
Douthwaite, A. H., and Trafford, J. A. P. (1960): *Brit. med. J.*, **ii**, 687.
——, ——, McGill, D. A. F., and Evans, I. E. (1961): *Ibid.*, **ii**, 6.
Elek, S. D., and Fleming, P. C. (1960): *Lancet*, **ii**, 569.
Evanson, J. M., and Sears, H. T. N. (1960): *Ibid.*, **ii**, 387.
Fairbrother, R. W., and Taylor, G. (1960): *Ibid.*, **ii**, 400.
——, —— (1961): *Ibid.*, **i**, 473.
Garrod, L. P. (1960a): *Brit. med. J.*, **i**, 527.
—— (1960b): *Ibid.*, **ii**, 1695.
Harington, M., Kincaid-Smith, P., and McMichael, J. (1959): *Ibid.*, **ii**, 969.
Hill, A. Bradford, *et al.* (1960): *Quart. J. Med.*, **29**, 597.
Hodge, J. V., McQueen, E. G., and Smirk, H. (1961): *Brit. med. J.*, **i**, 1.
Jackson, R. C., *et al.* (1960): *Ibid.*, **ii**, 1909.
Jevons, M. P. (1961): *Ibid.*, **i**, 124.
Kellaway, G. (1959): *Lancet*, **ii**, 768.
Kitchin, A., Lowther, C. P., and Turner, R. W. D. (1961): *Ibid.*, **i**, 143.
Knox, R. (1961): *Brit. med. J.*, **i**, 126.
Knudsen, E. T., *et al.* (1961): *Ibid.*, **ii**, 197.
Leishman, A. W. D., Matthews, H. L., and Smith, A. J. (1961): *Lancet*, **ii**, 4.
McLachlin, A., *et al.* (1960): *Ann. Surg.*, **152**, 678.
McMichael, J., and Parry, E. H. O. (1960): *Lancet*, **ii**, 991.
Medical Research Council (1959): *Brit. med. J.*, **i**, 803.
Merrill, J. P., *et al.* (1960): *New Engl. J. Med.*, **262**, 1251.
Milne, M. D., *et al.* (1960): 'Recent Advances in Renal Disease', London, p. 35.
Munck, O., Kristensen, H. S., and Lassen, H. C. A. (1961): *Lancet*, **i**, 66.
Murray, J. E., Merrill, J. P., and Harrison, J. H. (1958): *Ann. Surg.*, **148**, 343.
Nagley, M. (1961): *Lancet*, **i**, 851.
Nichol, E. S., *et al.* (1959): *Ann. intern. Med.*, **50**, 1158.
Owren, P. A. (1961): In 'Thrombosis and Anticoagulant Therapy', edited by W. Walker, Edinburgh, p. 35.
Pickering, G., *et al.* (1961): 'The Treatment of Hypertension', Springfield, Ill.
Rolinson, G. N. (1961): *Brit. med. J.*, **i**, 125.
——, and Stevens, S. (1961): *Ibid.*, **ii**, 191.
——, ——, *et al.* (1960): *Lancet*, **ii**, 564.
Ross, J. Cosbie, *et al.* (1961): *The Practitioner*, **187**, 312.
Scribner, B. H., *et al.* (1960): *Trans-Amer. Soc. Artificial Internal Organs*, **6**, 114.
Sevitt, S., and Gallagher, N. G. (1959): *Lancet*, **ii**, 981.
Shaw, D. A. (1960): 'The Pathogenesis and Treatment of Occlusive Arterial Disease', London.
Singer, A., and Rob, C. (1960): *Brit. med. J.*, **ii**, 633.
Smith, G. (1960): *Ibid.*, **ii**, 1154.
Stewart, G. T., Nixon, H. H., and Coles, H. M. T. (1960): *Ibid.*, **ii**, 703.
——, *et al.* (1961): *Ibid.*, **ii**, 200.
Taylor, S. H., and Donald, K. W. (1960): *Lancet*, **ii**, 389.
Turnbull, A. C. (1960): *Brit. med. J.*, **ii**, 1154.
Venning, E. H., *et al.* (1959): *J. clin. Endocr.*, **19**, 403.
Williamson, G. M., Morrison, J. K., and Stevens, K. J. (1961): *Lancet*, **i**, 847.
Wilson, C. (1960): 'Recent Advances in Renal Disease', London, p. 220.
——, and Abrahams, D. G. (1957): *Brit. med. Bull.*, **13**, 39.
Wood, P. (1961): *Brit. med. J.*, **i**, 1779.
Woodruff, M. F. A., *et al.* (1961): *Lancet*, **i**, 1245.

ADVANCES IN SURGERY

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A DISCUSSION of advances in surgery made during the last year is a difficult undertaking. To judge the future, prophetic faculties are needed, and we have to admit that it was never among the surgeon's gifts to predict and evaluate the future development of his specialty. On the occasion of the quincentenary of the University of Basle, a commemorative volume was published, entitled 'Teaching and Research at the University of Basel at the Time of its 500th Anniversary'. For this I compiled an anthology of blunders in predictions made by respected leaders of our profession when asked to state their opinion on the future prospects of surgery. Judging from the results of this valuable exercise, one would be justified in concluding that the lack of such historical foresight is natural for an otherwise gifted surgeon's mind.

Fortunately, misjudgments only become evident after a number of years, and therefore I feel I can proceed without immediate risk with an evaluation of the advances in surgery in the recent past.

PRE- AND POST-OPERATIVE CARE

Improvements in pre- and post-operative treatment and in the prevention and management of shock during operation are rightly regarded as decisive advances. Indeed, they are far more important than those achieved in operative technique. Many articles, however, still omit critical evaluation, and neglect clinical findings. It is for this reason that Francis Moore's book on 'The Metabolic Care of the Surgical Patient' probably represents the most important surgical publication of recent years, offering, as it does, a careful and critical presentation founded on long experience. Particularly is he to be commended for pointing out the insufficiency of many investigations, as well as the scientific inaccuracy of some of our medical terms, such as 'stress reaction' and others.

The alarming aspects of modern '*hospitalism*' are still with us. Wound infections are apparently of lesser importance today than 'staphylomycosis' of the air- and food-passages. The reason for this change appears to be the re-establishment of the rigid asepsis of former times. Meanwhile, however, ulcerative enterocolitis and—even more so—staphylococcal pneumonia are still almost out of reach of effective therapy. Now that the isolation of the penicillin molecule has been achieved, however, there is hope that the problem of penicillin resistance, particularly in the case of the staphylococcus, may be overcome.

In cases of *severe burns* wound infection today presents the greatest problem, now that the treatment of shock has been standardized and is

universally applied. The mortality rate among patients with extensive burns, especially those of middle or old age, is still high. This is almost exclusively due to infection—mostly staphylococcal.

Perhaps the most impressive evidence of the influence of modern preoperative treatment upon the ultimate results of surgical intervention is that provided by the results of *surgery in elderly patients*. The immediate effects of elective surgery are decisively improved; practically no age limit exists for major operations in the abdominal cavity, such as removal of intestinal carcinoma; even extensive interventions in the thoracic cavity are endured without prohibitive mortality. Only emergency operations in old age still offer a depressing outlook, and during the last ten years only a negligible reduction of postoperative mortality has been achieved. For the time being we do not know how this situation could be improved. The unfavourable outlook of ileus and intestinal perforation in elderly people weighs heavily in the mortality statistics of surgical departments and these conditions will get worse with the increasing percentage of geriatric patients in our hospitals.

The treatment of *tetanus* could be improved by combining continued application of curare and artificial respiration, sometimes combined with hypothermia. In cases which have previously had active immunization, an 'injection de rappel' is all that is required; in all others simultaneous active and passive immunization are advised.

In spite of the tremendous progress in cardiovascular surgery, the operation for *massive lung embolism* has tended to be forgotten, but there has been renewed interest in it on the Continent. In some of these cases heart failure may not set in for several hours, this means that careful preparation for surgical intervention is possible and the chances of success thereby increased.

HIATUS HERNIA

Symptoms of sliding hernia of the œsophageal hiatus are today considered to be due to reflux œsophagitis rather than to obstruction. Only reflux œsophagitis justifies surgical intervention. Methods to prevent regurgitation of the gastric juice seem to give far better results than those involving narrowing of the hiatus (hernioplasty).

THE BILIARY TRACT

Plastic operations on the bile ducts.—A large and increasing number of reports have dealt with this problem. It is now clear that there is no evidence to support the previously held view that in operating for stenosis or post-traumatic obliteration of the hepatic and common bile ducts lasting success can be obtained only if it is possible to join the stumps. Implantation of the central hepatic or common duct, respectively, into the duodenum has proved just as satisfactory, whereas duct implantation into an excluded jejunal loop seems to be definitely inferior in its end-results. Hepato-jejunostomy (Longmire) or similar procedures which join the left

branch of the hepatic duct with the intestinal tract seldom prove satisfactory because usually at the time of the operation obstructive liver cirrhosis is already present in an advanced stage: as a result of the operation having usually been preceded by several plastic operations on the extra-hepatic bile ducts. During this period liver cirrhosis can progress independently, whether or not the hepatic ducts have been surgically decompressed.

Cholangiography during operation has become a routine method for the identification of stones or stenosis of the bile passages. The great advantage of this technique is that open exploration of the common duct in cases of cholelithiasis is no longer based upon theory—but upon fact. In some cases, however, it may be impossible to differentiate between a stone and an air-bubble in the cholangiogram; it is also unjustifiable to look on a pointed termination to the common duct as an indication of inflammation in the papilla of Vater. *Manometry of the biliary tract* (cholangio-manometry) is also liable to misinterpretations unless care is exercised.

A word of warning must be issued against the large number of cases in which a diagnosis of stenosis of the sphincter of Oddi is now being made, followed by operation. This trend seems to neglect the experience that the majority of cases of inflammatory disease of the papilla heal without further symptoms once the cholelithiasis has been adequately operated upon. When operation is indicated no agreement has yet been reached on the question whether transduodenal sphincterotomy or choledocho-duodenostomy gives the better results. Personally I prefer choledocho-duodenostomy, being the less dangerous method.

Intraoperative endoscopic exploration of the common duct promises to be of practical value. The apparatus is not too complicated, and misinterpretation of the picture obtained is rare. On the other hand, the instrument in its present shape is so large that it may be difficult to examine a narrow bile duct without endangering its wall.

THE PANCREAS

Surgery of the pancreas remains a problem in spite of thirty years' endeavour to refine the operative technique. Chronic pancreatitis with an enlarged ductal system seems to offer reasonably good chances for surgical treatment, by using the different forms of pancreato-jejunostomy.

Ellison and Zollinger have reported that a certain type of tumour of the islets of Langerhans is occasionally the cause of persistent anomalies of the gastric and duodenal secretions, thus causing, particularly in the third part of the duodenum, ulcer formation of the recurrent type often referred to as 'surgically incurable' (such an ulcer, of course, is just as incurable by conservative treatment!). The majority of these non-insulin-producing tumours are malignant and offer the same poor prognosis as all malignant growths of the pancreas.

GASTRIC AND DUODENAL SURGERY

So far no consensus of opinion has been reached as to whether resection

of *chronic gastric and duodenal ulcer* should include vagotomy. By diminishing gastric secretion this operation undoubtedly reduces the tendency to ulcer formation, but it is too often forgotten that it also interferes with intestinal peristalsis, especially in elderly people. Symptoms of meteorism may trouble the patient severely—and for quite a long time in some cases. What can be said quite definitely, however, is that *permanent* changes in secretion do not occur after radical vagotomy. Cases have been reported in which resection of the œsophagus, with the accompanying unavoidable high vagotomy (certainly with all branches and interconnexions of the vagi totally removed), was performed, and in some of which anacidity changed to normal acidity within two to three years.

The extent of gastric resection has become the topic of renewed discussion as a result of the proposal to remove only the distal half of the stomach and to perform vagotomy in addition. It seems likely that in the majority of ulcer cases the final results of a two-thirds resection may likewise be achieved with hemigastrectomy, even without vagotomy. It should be kept in mind, however, that preoperative values of acidity must not influence the extent of resection. Ulcers occasionally recur after extensive resections in cases with moderate preoperative hyperacidity. On the other hand, high hyperacidity can change into anacidity after hemigastrectomy.

So-called 'juxta-œsophageal' ulcers tend to degenerate into malignancy. In penetrating cases the operation of choice is resection of the upper half of the stomach, followed by œsophago-antrotomy, or œsophago-jejuno-antrotomy.

Experience with radical operations for *carcinoma of the fundus* of the stomach has proved the advantage of a preserved antrum in the process of food absorption. Total gastrectomy, customarily performed in cases of growths situated high up in the fundus, has been followed by the well-known disturbances in the absorption of fat, protein and iron which are hard to relieve. Preservation of the antrum alleviates these intestinal disorders considerably. It should be added, however, that these clinical findings so far lack confirmation by experimental physiology.

In some advanced cases of penetrating duodenal ulcer, especially when located on the posterior wall, resection was for a time regarded as technically too difficult and too hazardous. This attitude has changed. By leaving the ulcer crater *in situ* and by closing the stump in an atypical manner, using mainly the mobilized anterior duodenal wall, resection is practically always possible. This technique also guards against injuries of the bile duct and the hepatic artery. If stump closure without tension is made impossible by too extensive resection of the anterior wall, end-to-side anastomosis between the duodenal stump and the first jejunal loop solves the technical problem in a satisfactory way. The same procedure can be successfully applied to the closure of chronic duodenal fistulas, following insufficiency of the stump closure.

In their enthusiastic praise of the Billroth I method, surgical reports of

recent years do not take into consideration the fact that not a few surgeons have some thirty years' experience with this operation. In fact, long-term observation of a large number of cases has shown that Billroth I is difficult to perform from the point of view of obtaining a sufficiently wide anastomosis in fat patients. Used in the surgical treatment of penetrating duodenal ulcers, for which it has also been recommended, the Billroth I technique is liable to be followed by a fair number of ulcers at the site of the anastomosis. Some British surgeons also blame the Billroth I method for the appearance of postoperative ulcer at the lesser curvature, but this complication seems rather to be caused by food retention, similar to the condition in those cases of vagotomy in which the post-vagotomy pylorospasm has not been circumvented by additional gastroenterostomy. Only a broad anastomosis is technically adequate, and the dumping syndrome need not be feared as a consequence, because eventually some kind of sphincter mechanism forms at the region of the anastomosis.

Unfortunately, no favourable development can be reported in the therapy of post-gastrectomy symptoms. Practically all efforts to eliminate the dumping syndrome by changing from Billroth I to Billroth II have been doomed to failure. Indeed, we are not even sure if rapid emptying of the stomach is the reason for these symptoms. Damage to the liver, which apparently develops occasionally in patients who have undergone gastric resection, presents a new factor in the evaluation of stomach resection, unpredictable in its consequences.

CEREBROVASCULAR SURGERY

In disorders of the cerebral blood supply vascular surgery has achieved remarkable results by by-passing and reopening the stenosed or occluded arteries. Extracranial lesions of the cerebral vessels are amenable to surgery if they are located at the origin of the left common carotid and the innominate artery. They are usually encountered in a multiple fashion (as the aortic arch syndrome) and can be treated by means of a by-pass, originating in the intrapericardial part of the ascending aorta. Only the future, however, will tell whether or not the flow of blood through the prosthesis is assured in spite of the sternal pressure. In cases of a short stenosis endarterectomy should be considered. To ensure an uninterrupted blood supply during the operation a temporary by-pass is applied. Complete occlusion of the artery, of course, makes the by-pass unnecessary.

Obliteration or stenosis of the *distal* part of the extracranial vessels may permit operative reopening, as, for instance, of the vertebral artery, if the lesion is located bilaterally at the junction of the subclavian and vertebral arteries. Endarterectomy done from the lumen of the incised subclavian artery is performed on one side only. Neither hypothermia nor temporary by-pass is needed.

Operative treatment of lesions of the *internal carotid artery* is promising only in cases of stenosis or occlusion of recent date; and even then estab-

lished neurological disorders can hardly ever be improved. The method of choice is endarterectomy. As a safeguard either hypothermia is used or preferably a temporary extra- or intra-vascular by-pass: i.e. either a by-pass from the subclavian artery to the distal part of the internal carotid artery, or the insertion of an intra-arterial plastic tube. A 'teflon' patch sutured into the incision prevents stenosis resulting from suturing of the incised wall of the vessel.

SURGERY OF THE AORTA

In the desperate situation of a *dissecting aneurysm* fenestration in the middle part of the descending aorta seems to be a suitable procedure, if the patient survives the initial shock. The operation is not too extensive. Although it helps in guiding the blood stream from the newly organized canal within the aortic wall into the normal lumen, the danger of a second rupture of the ascending aorta always remains.

The replacement or by-passing of the *abdominal aorta* in the treatment of *sclerotic stenosis* or *aneurysmal lesions* has become a well-established domain of vascular surgery. 'Teflon' or 'dacron' prosthesis has helped to make this gratifying development possible and it seems that these materials have solved the problem of plastic replacement.

PERIPHERAL VASCULAR SURGERY

The experience of recent years has allowed for better judgment in the selection of cases for vascular surgery of the peripheral arteries.

Under certain conditions, *stenosis of the renal artery*, which is seen more often today than formerly, can be successfully treated by endarterectomy or a by-pass. For this reason selective angiography of the renal arteries should be performed in all young patients with hypertension if signs of coarctation of the aorta are absent. Cases of unilateral or bilateral stenosis of the renal arteries—whether or not combined with arteriopathy of the aortic artery or its peripheral branches—may be a promising objective of surgery, provided the hypertension is not of long standing. Poor renal function is not a contraindication, as it will improve following the increased circulation. In cases of unilateral lesions of the renal artery return of blood pressure and renal function to normal can be expected only if the other kidney is not secondarily involved. The surgical technique consists of endarterectomy, or aorto-renal by-pass for cases of additional aortic disease if a more extensive destruction of the arterial wall exists.

In arteriosclerotic disease of the *lower extremities* operation is clearly indicated in early ulceration, and if the patient has pains even when resting. Intermittent claudication leading to marked social disability may make an operation desirable; this kind of elective surgery must be more liberally recommended in lesions of the aorto-iliac region than in the femoro-popliteal. Advanced age, poor general condition, advanced emphysema, poor kidney function and a history of cerebral episodes and mental disorders are contraindications.

ADVANCES IN OBSTETRICS AND GYNÆCOLOGY

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In the United Kingdom and Eire the day of the amateur in obstetrics is almost over and in my view this represents the biggest advance in the last twenty-five years. Only recently in my Unit, however, we had a piece of history admitted from the district; a case of 'failed forceps'. The cervix was split, the rectum torn and the mother was in a state of severe shock; the baby was dead *in utero*. The whole Unit (postgraduates, students and midwives) gathered silently to see this spectacle. In his Ingleby Lecture in Birmingham last year Baird (1960) recorded:

> 'In the years 1925-34, 426 cases were admitted to the Glasgow Royal Maternity Hospital after an unsuccessful attempt by the general practitioner to deliver with forceps in the patient's home. The maternal mortality was 14 per cent. During the years 1932-34 (when the writer was a student in Glasgow) "failed forceps" cases were sent in by 121 practitioners . . . 9 by one doctor alone'.

The bad old days are gone in Glasgow, and in Birmingham too, and we can see the extent of the improvement by recording that about once a week one of our former obstetrical house surgeons, now a general practitioner-obstetrician, will lift a baby's head over the perineum using local anæsthesia, whilst our unit has not admitted an 'F.F.O.' (failed forceps 'outside') with lacerations and shock for years. The prompt transfer of borderline and doubtful cases to hospital early in labour and better selection of cases for domiciliary practice both serve to keep the 'F.F.O.' as an interesting historical term.

TOXÆMIA OF PREGNANCY

When we meet colleagues who are interested in obstetrics at postgraduate courses it is our custom in Birmingham to end the course with a free-for-all, with my colleagues on the staff attempting to answer questions. A common question is: 'Would the panel tell us where we G.P.-obstetricians commonly fail? What clinical "gaffe" is commonest?'. The panel of practising obstetrician-lecturers never fails to surprise the class with the unanimity of its answers:—

(1) You are not fully aware of the dangers of toxæmia.
(2) You are holding your cases of toxæmia far too long at home or in your general practitioner units.
(3) You are masking your cases of toxæmia with diuretics and ganglion-blocking drugs.
(4) Your book-keeping is failing.

This last answer implies that a patient booked for modern antenatal care must not be allowed to default. That is to say, if Mrs. X's card on the desk says 'Mrs. X antenatal visit due' and she does not turn up, then down

she goes for a visit on the practitioner's rounds that very day. We all know that mothers with children offer a wonderful variety of perfectly reasonable excuses for non-attendance but none is finally acceptable, and certainly none will relieve the gloom of the obstetrician compelled to snatch a tiny infant from the mother's womb to prevent the mother from dying of eclampsia or anuria.

On the subject of modern antenatal requirements may I recommend the best four shillingsworth in obstetrical literature: 'Report on Confidential Enquiries into Maternal Deaths in England and Wales, 1955-1957' (Ministry of Health, 1960). Referring to toxæmia for example, the committee remark that 'the intervals at which patients were seen appeared to be prescribed by an inflexible routine and were often too long'. There follows a list of examples of patients with early and obvious signs of toxæmia being advised to take life gently and report in two or three weeks! Lack of obstetrical knowledge led others in good conscience to make serious errors. For example, patients were visited daily at their home and allowed to stay there at rest with a blood pressure of 170/110 mm. Hg, only to be sent to hospital when protein boiled solid in the urine after intervals of six or even nine weeks from the onset of the disease. Resultant eclampsia and anuria in these cases are, of course, clearly preventable. The analysis of the problem led to this sentence: '*Of* 171 *maternal deaths from pre-eclampsia, toxæmia and eclampsia, death was thought to be avoidable in* 90 *cases*'.

In 1961 shall we be able to record any advance which might show improvement on this Report, or shall we once again have 75 deaths laid at the door of the hospital and 121 at the door of domiciliary midwifery? As in any obstetrical problem, I think we may expect better results from an increasing awareness among G.P.-obstetricians and specialists alike that the disease still kills many mothers and many more babies. Over the period 1952-57 covered by the 'Confidential Report', although the percentage of avoidable factors has risen from 52 per cent. (1952-54) to 54.8 per cent. (1955-57), nevertheless the actual number of deaths with avoidable factors has fallen: a grain of comfort at any rate and a challenge to those concerned with the care of the mother and her child.

THE VACUUM EXTRACTOR (VENTOUSE)

The Malmström suction-cup technique (Malmström, 1954) has been under trial in the United Kingdom, especially by J. A. H. Chalmers (Chalmers and Fothergill, 1960; Fothergill and Chalmers, 1961), my colleague in Worcester. The principle of 'sucking out the head' is old, but the modern instrument has stimulated interest especially on the Continent. E. W. L. Thompson, formerly Master of the Rotunda, also considers that the ventouse is worthy of an extended trial (Thompson, 1960). Some of the indications and contraindications are shown in table I.

Full dilatation of the cervix although favourable is not a necessary prerequisite, for the small suction cup can be affixed and gentle pulls with a

slight side-to-side action used to stimulate a better quality of uterine contraction and so full dilatation of the cervix. The danger of easing the head through a three-quarters dilated cervix is that above the cervix there may be a constriction ring requiring immediate deep general anæsthesia if the child's shoulders are to be delivered and stillbirth avoided. The manœuvre of delivery through an incompletely dilated cervix is, of course, for the experienced obstetrician working next to a prepared Cæsarean section theatre including the services of an expert anæsthetist. Used with these safeguards the ventouse may occasionally save a Cæsarean section with its risk of maternal morbidity and later obstetrical sequelæ, especially a repeat

Favourable	*Unfavourable*
(1) A mature child	A premature child
(2) No fœtal distress	Fœtal distress
(3) No bony disproportion	Bony disproportion
(4) Cephalic presentation: vertex low in pelvis	High head, just in pelvis: breech unfavourable but not impossible
(5) Fully dilated cervix	Cervix not quite fully dilated
(6) Occipito-anterior	Face: danger to eye
(7) Occipito-transverse } Rotation with suction Occipito-posterior } pull and torsion	

TABLE I.—Indications and contraindications for the use of the ventouse.

section. The instrument is not difficult to use but, of course, preliminary instruction must be obtained from an expert.

At the moment the ventouse is not used except in hospital practice, but for the future I believe that the instrument will on occasion be used in G.P.-obstetric units in preference to low forceps. One must also envisage the use of the ventouse by a skilled and well-instructed midwife in, for example, the rural areas of Central Africa or the Sudan. It could well be life saving and used, *faute de mieux*, without medical supervision. In case of failure her patient would be in no great danger and the child little the worse apart from the usual temporary 'suction' caput or 'chignon'.

THE PREVENTION OF CERVICAL CARCINOMA

We now have in our hands a method of preventing cancer of the cervix which offers a challenge to the doctor in general and hospital practice.

A recent report by Boyes, Fidler and Lock (1961) from British Columbia, where general practice is at a high level of efficiency, records that many family doctors are using a 'free' cytology service. As a result there has already been a significant fall in the incidence of cervical cancer in the Province. The family doctor may say to Mrs. Brown after, say, immunization of her child against poliomyelitis: 'Don't you think that it's about time you joined the list for regular cancer checks?'. Already well-informed about cancer tests by radio, television, newspaper and even public window displays, Mrs. Brown knows that her doctor is offering her protection against cancer. Accordingly, she submits there and then to speculum examination

and the first of her yearly scrape-smears taken from the ecto-cervix. In due course the smear is sent to a cancer centre in Vancouver (which is financially Province-aided) where an expert team search for the tell-tale cells.

It is important to remember that the search is not primarily for clinical carcinoma although occasionally an unsuspected carcinoma is discovered. The chief target is carcinoma-in-situ variously described as non-invasive carcinoma or even 'sugar icing' carcinoma—a useful descriptive term. This is carcinoma in its non-invasive, non-metastasizing form and it is curable.

A pilot test in Birmingham.—We have screened every gynæcological patient in our unit by the method of cytology since 1952 and since 1958 every obstetrical patient, so that now we know what to expect from applying the test to a hospital patient with an apparently quite normal cervix:—

	Per 1000 *patients*
Positive smear leading to histological proof of carcinoma-in-situ	4
Surprise' detection of invasive carcinoma	1
'Surprise' detection of dyskariosis (abnormal nuclei) later found to become positive	1
'Surprise' detection of carcinoma of corpus uteri	1

In round figures, excluding cell smears from obvious carcinoma of the cervix, but including the occasional surprise positive smear from 'hidden' carcinoma of the cervix or corpus, the clinician who uses cytology can xpect to 'net' a total of about one per cent. In Edinburgh, family doctors working with Anderson and Kellar 'netted' positive smears (surprise positives) in 1.5 per cent. of cases (College of General Practitioners, 1958).

THERAPY OF CARCINOMA-IN-SITU

It is known that within five, ten or more years at least a third of patients with carcinoma-in-situ will have invasive, perhaps lethal, carcinoma (Petersen, 1955). Boyes and his colleagues (1961) and Fidler *et al.* (1957) suggest a figure nearer to 50 per cent. The latent period of several years, however, offers no reassurance to the patient or to the gynæcologist responsible for her clinical care. As soon as he sees a positive smear-report he wants to know if there is coexistent invasive carcinoma as well as 'in-situ' carcinoma: i.e. there is urgent need of a cone biopsy of the cervix as well as curettage of the canal and uterine cavity.

Following the cone biopsy (necessary for histological proof) hysterectomy was formerly routine in our group but over the last six years we have tried to be as conservative as possible, at least to the limit we considered to be quite safe. Knowledge of the scope of conservative therapy we knew would be of special value in young women in their 30's who wish to have children. Knowledge of the safety of removing only a small piece of cervix is also important for older women who might well dread a hysterectomy, in the belief that loss of the uterus might destroy a happy marital relationship—and this despite all reassurances to the contrary by her doctor and gynæcologist.

At the moment we treat 8 out of 10 of our patients simply by using a

sharp knife to cut a cone biopsy from the cervix, and we believe that finally, as our experience grows, only 10 per cent. or less will come to hysterectomy. The operation is a kind of 'baby' Sturmdorf amputation of the cervix including the ecto-cervix and lower canal in the shape of a dunce's cap; this neither sterilizes the patient nor causes abortion or premature labour. We tell our patients and, even more firmly, anxious husbands, that our conservative policy has proved perfectly safe and effective but we require that (1) the patient reports at intervals over the following years, (2) if after cone biopsy there is (cytological) evidence that carcinoma-in-situ is not completely removed she must submit to hysterectomy. To the reasonable question 'Would you agree to conservative treatment if we were discussing your wife and not mine?', I give a clear affirmative.

Conservative therapy of carcinoma-in-situ is thus an advance in our knowledge and it adds power to the medical propaganda which must precede any community-effort in cancer prevention by cytology. That is to say, we can now offer a woman a test to detect pre-cancer which itself can be cured by a simple operation on the cervix.

THE KEY TO THE METHOD

Which of us, the family doctor, the pathologist, the gynæcologist, or the cytologist is the linch-pin in a project to reduce cervical cancer in the community? All depend on each other but it is the cyto-technician or cytologist on whose patient and time-consuming microscopic search for the 'tell-tale' cells the whole scheme rests. Unfortunately, they are still few in number and training is very exacting. Are the cytologists ever wrong in their opinion on cell smears? Certainly they are, but so seldom that given a positive smear, action can be taken at once: i.e. admission, curettage and cervical biopsy. In our experience there is over a 95 per cent. chance of finding the source of the 'malignant' cell at histology.

In summary, then, I take the view that we can now move with confidence from the *therapy* of cervical invasive cancer to its *active prevention*—a big step forward. Moreover, after much thought and a personal review of Continental, American and Canadian work in this field I consider that we have been unduly worried about cancerophobia. The modern patient with her women's magazines, her television and 'doctor in the house' type of film is quite able to grasp the facts about a test aimed at cancer-prevention. If it is endorsed by her own family doctor whom she knows and trusts then she may submit to the test not only once but at regular intervals.

The future.—In the next five years I envisage a widespread use of cytology tests with active cytology departments in local hospitals under the direction of gynæcological pathologists and the clinical direction of experienced gynæcologists. There will, of course, be problems of finance. In British Columbia the doctor who makes the test is paid on a fee-for-service basis directly by the patient; our National Health Service excludes this method. As the 'screening programme' gathers momentum the financial

question will have to be faced, but I do not see this as insuperable in a worth-while experiment in community health aimed at the prevention of a terrible disease, carcinoma of the cervix. For further study I recommend the remarkable report from Memphis by Kaiser, Erickson and their colleagues (1960) based on tests taken from 151,000 women.

COLPOSCOPY

This is carried out by means of a type of binocular instrument used initially by Hinselman in Germany over thirty years ago. With the evolution of the cytology technique it is again being used in gynæcology to magnify the ectocervix. The cervix is first cleared of mucus and prepared by the application of dilute acetic acid. The cervix may also be stained for glycogen with iodine, thereby outlining areas on the portio vaginalis lacking normal differentiated epithelium. An expert can quickly identify areas of abnormal or defective epithelium. He may then subject abnormal or 'suspected' areas to biopsy or he may apply the eyepiece directly to the cervix: so-called direct colposcopy or colpo-microscopy. This instrument can magnify surface epithelium up to 70 diameters, presenting a flat histological picture several epithelial layers thick. With direct colposcopy patience is required on the part of the patient, for the eyepiece of the direct colposcope passes per vaginam to make contact with the cervix which is then studied field by field. Areas of cervical epithelium can actually be labelled as pathological; without cone biopsy, however, there is no guarantee that coexistent carcinoma might not also be present.

The method of indirect (binocular) colposcopy has been used successfully by gynæcologists who lack a cytology service, to assist in the search for carcinoma-in-situ or even micro-carcinoma; for the clinician in a busy outpatient department, however, it is slow and cumbersome and offers few practical advantages over cytology. Nevertheless, we regard the instrument as an advance since it can be used by the gynæcologist working on his own. Patient study of the cervix will reveal pathological changes not obvious to the naked eye. Finally, the instrument allows the research worker to study pathological tissue 'in situ'.

CULDOSCOPY

This instrument, which allows inspection of the pelvic organs, resembles a cystoscope. Intraperitoneal air and positioning of the patient allow a remarkable view of the pelvis.

Miss B., aged 28 and unmarried, a nursing sister in a busy hospital, complained of increasing prostration from dysmenorrhœa. Physical findings amounted to some tenderness in the pouch of Douglas. The clinical findings suggested a diagnosis of endometriosis and the problem arose as to whether exploratory laparotomy was justified, or whether (expensive) progesterones should be prescribed without confirmation of the diagnosis?

The patient was anæsthetized and intubated. Following pelvic examination and exploration of the uterine cavity, she was turned over on her face and mounted on a crutch so that the knee-elbow position was easily maintained. The culdoscope was then pushed gently through the posterior fornix, applying the sharp nose of the trocar close to the posterior wall of the uterus. This revealed the presence of endo-

metriosis: numerous small black dots were clearly seen studded over the utero-sacral ligaments. A clear view was obtained of the (normal) ovaries and Fallopian tubes, thus excluding gross chronic pelvic infection (tuberculosis). Carbon dioxide passed into the uterus was observed as it bubbled through the fimbriæ.

The culdoscope was thus of value in this case in that (a) it helped to verify the clinical diagnosis without laparotomy; (b) it allowed us to spend a great deal of National Health Service money on norethisterone, providing the patient with eighteen months of relief (and incidentally providing her hospital with eighteen months of excellent service!). From the patient's point of view she was relieved to have the exact diagnosis, no doubt having suffered quite unjustly from: 'She's getting a bit neurotic for a nurse . . . even fusses about her dysmenorrhœa!'.

In the hands of an experienced gynæcologist the culdoscope is safe, but anæsthesia has to be in the hands of an expert. I have found the instrument of especial value when for various reasons I wanted to avoid laparotomy: for example, when I felt the patient was already introspective and anxious. Culdoscopy does not completely exclude pathological change in the pelvis, but it is of value to the clinician to have viewed the normal ovaries and tubes and explored visually as well as digitally the pouch of Douglas.

In recent years in Birmingham lack of work in the West Indies and shortage of labour in the Midlands have led to the arrival of many West Indians. This has produced gynæcology reminiscent of the pre-antibiotic era: chronic tubo-ovarian inflammatory disease with its sequelæ of (dreaded) infertility and dyspareunia. Just after the last war we observed a similar run of newcomers with diseases of the pelvis; they came from D.P. ('displaced person') camps and many had been involved in the horrors of Europe in the 1939-45 era. For them we coined the term 'refugee pelvis'. In both of these social groups, especially the latter, tubo-ovarian disease often of tuberculous nature was not uncommon. In the case of these patients from the West Indies, who are with us in increasing numbers, for precision of diagnosis and prognosis I have found the culdoscope a valuable addition to ordinary clinical methods. For a more detailed report on the culdoscope T. N. A. Jeffcoate's study (1960) is commended.

THROMBO-EMBOLISM

Death from embolism accounts for every third death in our gynæcological hospital. In obstetrics the 'Confidential Enquiries into Maternal Deaths' tell a similar tale; it now compares with criminal abortion among the lethal complications of pregnancy. By no means all deaths are available for recording but these two 'Confidential Reports' (Ministry of Health, 1957, 1960) reveal that in England and Wales the number of deaths from pulmonary embolism during pregnancy was 138 in 1952-54, and 157 in 1955-57. As clinicians what can we say about the problem?

Despite the closest attention to calf and leg inspection before and after operation or childbirth all we can claim is that nowadays a severely damaged venous return is less common than formerly whilst, apart from pelvic neoplasm, we seldom see a classical white leg. Early diagnosis and anticoagulation must be accepted as an advance. Embolism, however, is still with us, killing young women who are often mothers of families.

All of us working with the threat of thrombosis hanging over our obstetric and gynæcological patients try to make a guess at the type of patient who may develop thrombosis either in the leg or pelvis. I suggest the following list of 'red' or 'amber' signals.

(1) *Red.*—Prolonged rest in bed because of pre-eclampsia, hypertension, twins, recurrent abortion; artificial rupture of the membranes—failed induction leading to Cæsarean section. *Expect thrombosis; watch for calf pain and tenderness.*

(2) *Amber.*—Previous leg thrombosis after surgery or bed rest; previous embolism in pregnancy or after delivery. *Expect a possible recurrence.*

(3) *Red.*—Sudden anæmia, e.g. from an abortion, with hæmoglobin 5 g. per 100 ml.; treated by transfusion followed by dilatation and curettage under general anæsthesia—recovery. *Expect calf pain within the next week; expect pulmonary embolus.*

(4) *Red.*—Serious cardiac disease, with complete bed rest for eighteen weeks and spontaneous delivery; post-partum hæmorrhage with hæmoglobin of 7 g. per 100 ml., and slow transfusion of packed cells. *Expect pulmonary embolism.*

(5) *Amber.*—Obesity with or without marked varicose veins; abdominal or pelvic surgery. *Expect thrombosis in legs or pelvis and possible pulmonary embolus.*

PREVENTION OF PULMONARY EMBOLISM

A report from Cambridge (D. G. Chalmers *et al.*, 1960) gives strong support to the proposition that, although patients receiving anticoagulants may develop deep femoral thrombosis and even a small embolism, they seldom die from a fatal embolism. These workers reported on 1,877 pelvic operations in which the expected fatal embolism rate was anticipated at 0.2 per cent. Using phenindione to lower prothrombin levels to 15 to 20 per cent. the incidence of fatal embolism fell to 0.4 per cent. The prophylactic use of anticoagulants did not exclude careful preparation of the patient for surgery, early ambulation or the use of elastic support for varicose veins of the legs. The cost in clinical effort in such a programme, however, must be measured. For example, from the third to the tenth day accurate estimation of venous blood levels of prothrombin and the gauging of dosage of phenindione is time-consuming for the occasional patient but for a whole ward it becomes the houseman's nightmare. Moreover, of the 1,877 Cambridge patients treated prophylactically, 57 suffered bleeding from operation sites and 26 of these required active treatment such as packs, and in 10 serious hæmorrhages required blood transfusions.

Prophylactic anticoagulation obviously requires a hospital team with the closest watch for oozing or even sharp hæmorrhage from a wound; blood must be available at short notice for transfusion. Consultation is required each day to decide on dosage until 'stability' is reached at between 15 and 30 per cent., and this is by no means always easy to achieve.

Further work of importance in the successful prophylaxis of pulmonary embolism has been reported by Sevitt and Gallagher (1959) from the Accident Hospital, Birmingham. They anticipate pulmonary emboli in older patients with fractures, especially of the hip. Lowering of prothrombin levels usually begins soon after the patient is admitted as an emergency and, of course, the most meticulous attention is given to the control of prothrombin levels.

At the moment, then, with fatal emboli now rated third among causes of death in obstetrics and gynæcology we can at least report that there is a good case for prophylactic treatment in selected patients and pelvic operations. We must, however, face a risk from hæmorrhage, pending the arrival of a safer form of anticoagulant, whilst the application of routine prophylaxis, as for example in pelvic surgery, involves a great deal of pains-taking work in the day-to-day control of prothrombin. If embolism should occur anticoagulation must be considered for periods of up to six months, patients attending as outpatients at intervals for control of prothrombin levels. Finally, my colleagues in the gynæcological and obstetric unit are engaged in an assay of the value of prophylaxis but it is too early to say if we are eliminating fatal pulmonary emboli on the scale of the Cambridge workers.

SUMMARY

Advances are recorded in the field of prevention in obstetrics. Of special importance is the gradual disappearance of the amateur from antenatal and operative obstetrics. Prevention of the grave sequelæ of toxæmia and thrombo-embolism is reviewed; a small step forward is recorded in each problem.

In operative obstetrics comment is made on the uses and future uses of the vacuum extractor in obstetrics.

In gynæcology the prevention of cervical cancer by vaginal cytology awaits funds and technicians before its final impact on the community can be assessed, but pilot studies are now complete and the results offer a challenge to the practitioner whether he works in a family practice or in hospital.

References

Baird, D. (1960): *Lancet*, **ii**, 577, 609.
Boyes, D. A., Fidler, H. K., and Lock, D. R. (1961): Personal communications and 'Proceedings of First International Congress of Exfoliative Cytology', Vienna, August 31, 1961.
Chalmers, D. G., *et al.* (1960): *Lancet*, **ii**, 220.
Chalmers, J. A. H., and Fothergill, R. J. (1960): *Proc. Roy. Soc. Med.*, **53**, 753.
——, and —— (1960): *Brit. med. J.*, **i**, 1684.
College of General Practitioners, South-east Scotland Faculty (1958): *Lancet*, **ii**, 895.
Fidler, H. K., Boyes, D. A., and Lock, D. R. (1957): *Canad. med. Ass. J.*, **77**, 79.
Fothergill, R. J., and Chalmers, J. A. (1961): *The Practitioner*, **186**, 559.
Jeffcoate, T. N. A. (1960): *J. Obstet. Gynæc. Brit. Emp.*, **67**, 529.
Kaiser, R. F., Erickson, C. C., Bennet, E. E., Gilliam, A. S., Graves, L. M. Walton, M., and Sprunt, D. (1960): *J. Nat. Cancer*, **25**, 863-881.
Malmström, T. (1954): *Acta obstet. gynec. scand.*, **33**, suppl. 4.
Ministry of Health (1957): 'Report on Confidential Enquiries into Maternal Deaths in England and Wales 1952-1954', H.M. Stationery Office, London.
—— (1960): 'Report on Confidential Enquiries into Maternal Deaths in England and Wales 1955-1957', H.M. Stationery Office, London.
Petersen, O. (1955): *Acta Radiol. Stockh.*, suppl. 127.
Sevitt, S., and Gallagher, N. G. (1959): *Lancet*, **ii**, 981.
Thompson, E. W. L. (1960): 'Clinical Report of the Rotunda Hospital, 1958-59', Dublin.

ADVANCES IN PÆDIATRICS

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'From inability to let well alone; from too much zeal for the new and contempt for what is old; from putting knowledge before wisdom, science before art, and cleverness before common sense, from treating patients as cases, and from making the cure of the disease more grievous than the endurance of the same, Good Lord, deliver us'.—Sir Robert Hutchison (1953).

Emphases within the field of Medicine are undergoing reorientation and redeployment. As the trend gains momentum, new specialties acquire popularity as old ones decline in favour. There are clinicians and administrators who visualize the disappearance in the not distant future of infectious diseases as a subject for detached special study. Academically, public health as it was once termed is variously described as social or preventive medicine. Pædiatrics has undergone considerable reorientation and is now customarily referred to as child health. This change is regarded in some circles as a prelude to the disappearance of pædiatrics and child health as a subject for separate study and practice.

In the main this view of child health is the outcome of the changing pattern of disease in infancy and childhood, and of the increasing extent to which scientific methods are being applied to the prevention and cure of disease in children no less than in adults. The view ignores the fact that pædiatrics is not a form of practice-specialty in the sense in which the term specialty is now commonly used. Pædiatric practice is concerned essentially with general medicine interpreted to include considerations of total physical, emotional and mental well-being; health and disease; prevention and cure; and of the individual, the family and the community. A holistic conception of the child is fundamental to the study and practice of pædiatrics, concerned as it is with the total development of the individual from before birth to the age of adolescence.

Contributions to 'Advances in Pædiatrics' in *The Practitioner* in recent years have dealt with pædiatric advances in connexion with nutritional and metabolic disease (Smellie, 1956a), developmental anomalies (Hay and Rickham, 1957), psychological illness (Lightwood, 1958), mental deficiency as an inborn error of metabolism (Hubble, 1959), immunization procedure and iatrogenic diseases (Schlesinger, 1960). Additional to these, other advances have been made on a broader front—advances less readily appreciated because of their less dramatically tangible character.

INTERNATIONAL AND OVERSEAS

Globally there are the firmly established links between pædiatrics in this and other countries represented in the International Pædiatric Association;

the periodic exchange of visits (sponsored in a number of instances by the British Council) between pædiatricians in the United Kingdom and their colleagues elsewhere in Europe and America; and the international interchange of students engaged in pædiatric research. The Institute of Child Health, London, together with the University of London Institute of Education, is taking part in a study of the growth patterns of healthy children being conducted jointly by research teams in Paris, Zurich, Stockholm, Brussels and Dakar (Institute of Child Health, 1959).

Within *the Commonwealth* progress in pædiatrics has been fostered through visits by British pædiatricians made at the instance of the Colonial Office, to places as widely separated as protectorates in West Africa and remote islands in the Pacific. For a number of years The Hospital for Sick Children, Great Ormond Street, has participated in an arrangement whereby senior registrars are seconded to the pædiatric services of Uganda; and nursing sisters from the Hospital volunteer to take temporary charge of the children's ward at the University Hospital, Kampala. In addition, a member of the consultant staff makes an annual visit to Uganda (Schlesinger, 1955). A further major contribution to international pædiatric advances is the postgraduate courses at the Institute of Child Health, London, and the University of Edinburgh attended by, amongst others, doctors from the Commonwealth countries and colonies. Other doctors from these same countries are attached for varying periods to university departments of child health elsewhere in the United Kingdom, financial assistance being provided in some instances by the British Council or the Commonwealth University Association. To an increasing extent university departments are becoming aware of the possibilities of furthering progress in pædiatrics by establishing working arrangements with activities overseas. This is evident in the secondment from the medical schools of Birmingham and Bristol of senior undergraduate students to Makerere and Ibadan for periods of three months or more.

NATIONAL

In the national field the importance of child health has been recognized in the appointment of consultant advisers in pædiatrics to the Home Office, the Colonial Office and the Ministries of Education and Health. Membership of national and other committees such as those responsible for the Platt Report (Ministry of Health and Central Health Services Council, 1959), the Cranbrook Report (Ministry of Health, 1959) and the recent report on 'The Prevention of Prematurity and the Care of the Premature Infant' (Ministry of Health and Central Health Services Council, 1961), included pædiatricians. In addition, the British Pædiatric Association has furnished information to those committees, to the Porritt Committee and to the Home Office departmental committee on artificial insemination.

The past few years have also seen a considerable expansion of the British Pædiatric Association. Extension of the membership, which now exceeds

220, has contributed to a wider exchange of experience; and has enabled the Association when consulted by central departments and organizations to express views representative of those held by pædiatricians with varied interests gained in a wide variety of circumstances.

CHILD HEALTH

Study of healthy development in infancy and childhood now occupies a leading place in the teaching and research of most departments of child health. Among recorded researches those of Professor R. S. Illingworth (1960) are noteworthy. A recent booklet sponsored by the Ministry of Health (Sheridan, 1960) deals with the assessment of attainments and makes use of Gessel grouping which must not, however, be too rigidly applied. Immunization procedures are under constant review and the findings of a recent symposium are the subject of a valuable report (Cannon *et al.*, 1960).

The health of children under 5 years of age and of schoolchildren bears testimony to the success which has attended the cumulative efforts of the maternity and infant welfare and the school health services. Undernutrition has almost disappeared and today's schoolchildren are taller, heavier, more robust and healthier than their predecessors (Ministry of Education, 1960). With the encouragement of the Ministry of Education a number of local education authorities are giving trial to schemes for the selective medical examination of pupils in preference to the routine inspection of children in the intermediate age-groups. Inspection of children starting school attendance has proved valuable in detecting previously unrecognized handicaps. Increasing attention is being focused on the need for earlier diagnosis and treatment of defective hearing, cerebral palsy and spina bifida. The fact that local education authorities are empowered to assess and make provision for handicapped children as young as 2 years of age is not as widely appreciated as it might be. Current new developments include the provision of small diagnostic nursery schools for young children whose educational subnormality is extremely severe, a boarding school for maladjusted children with communication difficulties, and a boarding school for maladjusted deaf children (Henderson, 1961).

INTEGRATION OF SERVICES

There is still room for closer cooperation between those engaged in family and hospital practice on the one hand and those in the employment of the statutory environmental services on the other (Burn, 1959). Health visitors participate in the outpatient and ward work of a limited number of hospital departments for children. The practice could be extended with advantage and there is a growing feeling in many quarters that closer working relationships should be encouraged between the general practitioner and the health visitor. Experience in a number of areas has shown that this can be attained with mutual goodwill (Roberts, 1953; Chalke and Fisher, 1957; Warin,

1959). Considerations of administration and local tradition arise but there are many family doctors who would welcome developments along these lines. The undoubted value of the health visitor would be enhanced were her responsibilities, in relation to children at least, to include those of home or district nurse. Miller and his colleagues (1960) have drawn attention to the difficulties arising from the lack of any clearly defined relationship between the health visitor and the family doctor, and their findings provide additional evidence in favour of the hope expressed by Spence and his colleagues (1954) that there will eventually be a merging of the work of the health visitor with that of the family practitioner.

Gradually, artificial distinctions between preventive and curative pædiatrics are disappearing. This is evident in the increasing number of general practitioners who arrange 'surgery' sessions for the exclusive attendance of mothers with their children of all ages; and in the employment of family doctors on a part-time basis at infant welfare sessions by a number of authorities. Whether in the 'surgery' or clinic, advice is given on management, feeding and diet; immunization procedures are carried out; and minor ailments receive attention. Local impetus has been given to this comprehensive evaluation of health in infancy and childhood by the activities of such societies as the Child Welfare Group at University College Hospital, London, and the Child Health Group developed at the instance of the University Department of Child Health, Bristol. It is the purpose of these and similar groups elsewhere, to recruit a membership representative of many aspects of child care and to facilitate exchange of views and experience between health visitors, midwives, district nurses, psychiatric social workers, probation officers, children's officers, teachers, family doctors and the medical members of local authority and hospital staffs.

HOSPITAL PHYSICIAN AND FAMILY DOCTOR

Progress in this process of integration of pædiatric interests has probably been slowest as between the hospital physician and the family doctor. Perhaps in no other branch of medicine is there so great a contrast between the clinical material seen in hospital and that seen in general practice. The contrast is being accentuated by the rapidly changing pattern of pædiatrics. One outcome is the trial being given to a variety of schemes designed to provide extended care of sick children in their own homes by more effective liaison between the domiciliary nursing, family doctor and consultant services (Gillet, 1954; Smellie, 1956b; Lightwood *et al.*, 1957). An inevitable result of these schemes has been the promotion of a better understanding of each other's point of view by the family doctor and the pædiatrician. The same result has been achieved where family doctors have been appointed as clinical assistants to a children's department in hospitals. Over twenty members of one provincial faculty of the College of General Practitioners have expressed a wish for appointments as pædiatric clinical

assistants (Sykes, 1961). Views are divided as to the desirability of the arrangement which admittedly is not everywhere either practicable or suitable. None the less there can be no denying that in a number of areas arrangements along these lines have been to the mutual advantage of pædiatrician and general practitioner—and to the advantage of sick children in, or attending, hospital.

CONSULTANT PÆDIATRIC SERVICES

Experience over the past few years has established that the increase in the number of pædiatricians has met a proven need. This is evident in the volume of work being undertaken by individual pædiatricians throughout the country. A major benefit to patients is the ease with which a domiciliary visit by a consultant known personally to the family doctor can be obtained, thus obviating the necessity to refer a child to a distant hospital for a second opinion. Furthermore, the wider distribution of pædiatricians has encouraged closer practical liaison between the hospital and local authority services for children. It cannot be maintained that consultant pædiatric services are as yet everywhere adequate. Appointments made on a population basis have not always taken sufficient account of the distances and time involved in visits made to widely dispersed homes and hospitals. In certain areas the pædiatrician cannot cope as efficiently as he would wish with the reasonable demands of hospitals, clinics, domiciliary visits and committee work. He is under constant pressure with few opportunities to review the results of his activities. Lack of time discourages if it does not actually render impossible comprehensive field research, and pædiatric progress suffers in consequence.

FIELD RESEARCH

That field research is of value has been shown by investigations initiated by the College of General Practitioners and its faculties. Subjects dealt with and having a bearing on child health have included measles (Watson, 1955; College of General Practitioners, 1956b); otitis media (Platt *et al.*, 1957), epidemic vomiting (College of General Practitioners, 1956a), epilepsy (Watts, 1960), congenital anomalies and asthma (College of General Practitioners, 1960), and the influence of home conditions on physical and mental health (MacLean, 1955). Continued development of field research by the family doctor, desirably in some circumstances in collaboration with pædiatricians and medical officers of health, holds out many possibilities (Burn, 1959). Two deserve particular mention. Research studies enable the family doctor to familiarize himself with the clinical and epidemiological features of new diseases of uncertain etiology, in anticipation of the time when his help will be needed to provide information for organized laboratory and other investigations (College of General Practitioners, 1956a). Equally important is the value of the advice concerning the content and conditions of family practice which the general practitioner can offer to the teachers of students preparing for professional life as family doctors (Spence *et al.*, 1954).

The catarrhal child has for long been a subject of interest to hospital physicians and general practitioners. Study of the findings of the Newcastle workers (Miller *et al.*, 1960), and of Fry (1961) reveals the benefit to pædiatric progress of parallel investigations in hospital and in the field. Tribute is paid in the first report of the Newcastle survey (Spence *et al.*, 1954) to the contribution of the general practitioner in the design and execution of research. Implementing the belief that 'a continuing process of mutual education . . . would make specialist and family doctor alike better equipped for the care of children', the University of Durham Department of Child Health has presented the results of studies in such subjects as intussusception (Spence and Court, 1950; Court and Knox, 1959), pertussis (Court *et al.*, 1953) and tuberculosis (Miller and McDougall, 1954) in ways designed to be of immediate practical value to the doctor busily engaged in general practice. At the present time family doctors in Edinburgh and Newcastle are collaborating with the local health authorities in a study planned by the Medical Research Council, into the spread of staphylococcal infections in families (Scott, 1961).

HOSPITAL SERVICES

Greatest uncertainty prevails in relation to hospital services for children. Certain published articles, including those dealing with the expansion of domiciliary care, have appealed to the administrator as evidence of a declining need for hospital beds for children. It has been effectively shown that the suggestion is inapplicable to the Newcastle area in particular (Taylor and Davidson, 1959) and lacks foundation when considered in relation to prevailing demands on children's hospitals in the provinces as a whole (Illingworth and Knowelden, 1961). Increasing demands are not limited to children's teaching hospitals and apply also to outpatient departments (Apley, 1961). The implications of the official attitude have to be considered in conjunction with prevailing trends.

There is the varying position with regard to infectious diseases hospitals. In some centres admissions to these hospitals include large numbers of children who until recently would have been automatically referred to and admitted by a children's department. It is no secret that a loose stool or evanescent spot can often secure telephone assurance of an infectious diseases cot or bed for a child whom a family doctor finds it inexpedient to submit to preliminary examination in the busy receiving room of a general hospital. The family doctor's attitude is often justified and, in reality, the challenge is to general hospitals to organize receiving-room arrangements suited to the needs of children. That a pædiatric opinion is desirable in connexion with many patients in infectious diseases hospitals is becoming more generally recognized. In more ways than one a pooling is taking place of the interests in children of the pædiatrician and the infectious diseases specialist. Present-day opinion favours the incorporation in sizeable children's hospitals and

departments, of a small isolation unit. Furthermore, it has been heard stated, although on what authority is uncertain, that a proportion of those appointed in the future to senior medical posts on the staffs of isolation hospitals may be required to have had previous pædiatric training. This would deal effectively with unsatisfactory situations obtaining in some infectious diseases hospitals.

CHILDREN'S HOSPITALS OR CHILDREN'S DEPARTMENTS?

With hospital planning so much to the fore the question inevitably arises as to whether new accommodation for children should take the form of a separate hospital or of a department within a general hospital. At least two well-known provincial children's hospitals are earmarked for eventual closure and replacement by departments in modernized general hospitals. It is not the purpose of this article to consider the arguments against and in favour of the policy, but any tendency to regard metropolitan experience as an infallible guide to provincial planning should be discouraged. There are other possible consequences requiring careful consideration.

Understandably, although not necessarily wisely or in the ultimate overall interests of patients, surgical and other sub-specialties are inclined to encourage the establishment of multiple dispersed small children's sections within their own units. With the disbandment of a children's hospital and the consequent disappearance of management and house committees interested primarily in the needs of children, increasing difficulty is experienced in effectively representing essential pædiatric requirements in the face of more glamorous competitive demands. This applies as much to staffing as to equipment and accommodation requirements. No matter how vigorously it may be denied, the fact remains that the senior administrative nursing staff of large general hospitals who are not themselves trained sick children's nurses, can on occasion betray inability or disinclination to appreciate the peculiar and heavy demands of a children's medical ward. As a result, instances occur of patients not receiving the degree of continuing, skilled supervision desirable; and of experienced sick children's trained ward sisters knowing undeserved, intense frustration. It is significant that not a few state registered nurses comment upon the virtual valuelessness to them of sporadic, fragmentary association with children's wards during their period of general training.

THE SICK CHILDREN'S NURSE

Emphasis of nursing considerations requires no apology. Whether it be in his preventive or curative work, in hospital or clinic, in connexion with the care of infant or child life, in great measure the pædiatrician is dependent for satisfactory results upon the skill and experience of his nursing colleagues. Changes and experiments are taking place in the training of nurses. There is a widespread, uneasy feeling that a movement is on foot to secure

the eventual abolition of the Supplementary State Register of Sick Children's Nurses. Certain children's hospitals have ceased to be training schools in their former capacity and are now providing nurses in general training with three months' experience in care of the sick child.

Charge duties in children's wards should only be entrusted to nurses who have undergone *special* training in the care of the sick child and it is vital that training facilities be preserved on an adequate scale. To meet the situation comprehensive training schemes have been organized in some centres. Training is of four years' duration and is provided by hospitals which are associated with one another for the purpose, training in care of the sick child being given at a children's hospital. At the end of her training the successful nurse is entitled to inclusion in both the State Register of General Trained Nurses and the Supplementary Register of Sick Children's Nurses. Elsewhere other approved training schemes are in operation which enable a general trained nurse to undergo training for a period varying between 13 and 15 months at a children's hospital in order to secure registration on the Register of Sick Children's Nurses.

It is vital to progress in pædiatric care that any adjustments in arrangements for nursing education should not contribute to a dearth of practising nurses with essential special training in care of the sick child. Shortage of staff imposes an intolerable burden on ward sisters, leading to exhaustion and strained human relations. Public recriminations can follow which achieve little beyond discouraging those who deserve encouragement and appreciation. The need is for employing authorities to accept responsibility for deficiencies in those services which they continue on a scale needed by babies and children in the community, but which impose excessive strain on a depleted professional nursing staff. Nor should it be forgotten that the members of a hospital nursing staff are the first to experience the repercussions of inadequacy of domestic help.

TRAINING OF THE MEDICAL STUDENT AND OTHERS

The pattern of progress in pædiatric instruction of the medical student has differed from teaching centre to teaching centre. In every medical school an improved standard of training in the care of the newborn has reflected the rewardingly close liaison existing between obstetricians and pædiatricians. With the establishment of neonatal units in maternity hospitals there are two possible undesirable eventualities to be kept in mind. There is the problem of ensuring that junior resident obstetrical staff have ample opportunity to gain experience in neonatal supervision. The opportunities are there but obstetrical duties tend to prevent advantage being taken of them despite stimulation from senior staff. Secondly, there is the need to consider the long-term interests of midwives who are devoting, or are prepared and anxious to devote, a considerable part of their active professional life to the care of the newly born baby. Except perhaps in the case of midwives of

senior status, prolonged absence from primarily maternal aspects of obstetrics involves disadvantages to the midwife not wholly offset by attendance at prescribed refresher courses. To say this is not to minimize the fundamental importance of neonatal care. There is evidence of the universally recognized importance of the subject in the recent appearance of an altogether outstanding textbook by Schaffer (1960) entitled 'Diseases of the Newborn'. No comparable publication has been produced since the classic work with the same title by von Reuss in 1920.

Common behaviour problems and the psychoses in children constitute another subject in which teaching departments are cooperating more closely with benefit to the student. Both pædiatrician and psychiatrist have interests in the subject, and the extent to which their interests overlap has given rise to uncertainty in the minds of students, practitioners and parents alike. Westmacott (1961) gives an interesting account of psychiatric social work in a pædiatric setting. Another significant event has been the evolution in Bristol of a Child and Family Guidance Service administered jointly by the City Council Education and Health Committees (Wofinden, 1960). The service represents a fusion of previously existing child guidance and anticipatory guidance services, and recognizes the extent to which emotional maladjustment in childhood is favoured by disturbed relations within the family circle. A subject referred to more commonly in the professional journals of the United States than in those of this country is the child who is the victim of cruelty in his own home. Elmer (1960) suggests that in the United States physicians and social workers are over-hesitant in accepting evidence of maltreatment in the home. In the United Kingdom pædiatric teaching departments are enlisting the active cooperation of family doctors, health visitors, children's officers and almoners to an increasing extent with the object of helping the student to appraise disturbed health—whether physical, emotional or mental—in terms of the environment from which sick children are drawn. An unfortunate feature of the present situation is the scarcity of almoners, and in particular of almoners with an inclination for work among children.

Those who would minimize the importance of general practice as one objective of undergraduate education are prone to emphasize that of graduates in medicine only one-third proceed to general practice. Be that as it may, a quarter to one-third of a family doctor's time is devoted to children. One difficulty of the teacher responsible for the student's introduction to the study of child life and health is to present facets of the subject in perspective. Training has to give experience in many conditions seen commonly in family practice but seldom in hospital; and has to ensure that the doctor of the future will recognize serious conditions, examples of which he will often see in the course of his clinical training in hospital, but only extremely rarely during the remainder of his active professional career.

Another difficulty with which the teacher of pædiatrics has to contend arises from the transfer of emphasis now taking place from the art to the science of medicine. As has been pointed out the doctor is not primarily a scientist (Thomson, 1960), and of all doctors it is incumbent upon those caring for children more than upon any others to exercise caution, consideration and humility when applying scientific advances whether for the purposes of investigation or treatment (Craig, 1960). In a recent address to engineers, the Duke of Edinburgh expressed the view that 'specialist training can give people the ability to make sweeping technological innovations, but it needs a broad and liberal education to enable people . . . to introduce the fruits of modern science to the best advantage of the people'. The warning is no less applicable to medical science.

EPILOGUE

These views imply no belittlement of the incalculable benefit to the child of recent advances in applied science, and no suggestion that an urgent need does not exist for large-scale scientific research in pædiatrics. None the less the holistic conception of child life within the family circle is fundamental to pædiatric thought; and a knowledge of human relations, and of the art of consultation and physical examination, must continue to provide the foundations of pædiatric teaching. It is not always easy to convey this approach at a time when increasing importance is being attached to 'skill of measurement' in the practice of medicine. Nor is pædiatric instruction along these lines helped by teaching elsewhere which leaves in the mind of the student an impression that the purpose, professional reward and content of general practice compare unfavourably with those of hospital or academic practice. Only teachers with experience of domiciliary consultant, or general, practice can correct the impression with conviction. If this is to be achieved a sufficiency of whole-time pædiatric teaching posts of all grades will require to be held by those who have had such experience. It is by the balanced presentation in correct perspective of developmental, sociological, epidemiological, clinical and scientific considerations that future advances in pædiatrics will bring greatest benefit to the greatest number of children in need.

The present age is one of administrative planning and multiplication of sub-specialties. It should not be complacently assumed that all prevailing trends are an assurance of uninterrupted progress in the future.

'We must . . . try to come to grips with the ancient tensions which lie between tradition and progress' (Neale, 1961).

References

Apley, J. (1961): *Lancet*, **i**, 1171.
Burn, J. L. (1959): 'Recent Advances in Public Health', London, chap. 8.
Cannon, D. A., Cockburn, W. C., Evans, D. G., and Parish, H. J. (1960): 'Proceedings of a Symposium on Immunization in Childhood', Edinburgh.
Chalke, H. D., and Fisher, M. (1957): *Lancet*, **ii**, 685.

College of General Practitioners (1956a): 'Research Newsletter No. 8, 1.
—— (1956b): *Ibid.*, Nos. 11 and 14.
—— (1960): 'Annual Report', p. 39.
Court, D., Jackson, H., and Knox, G. (1953): *Lancet*, **ii**, 1057.
——, and Knox, G. (1959): *Brit. med. J.*, **ii**, 408.
Craig, W. S. (1960): *Acta med. Acad. Sci. hung.*, **15**, 65.
Elmer, E. (1960): *Social Work*, October, p. 98.
Fry, J. (1961): 'The Catarrhal Child', London.
Gillet, J. A. (1954): *Brit. med. J.*, **i**, 684.
Hay, J. A., and Rickham, P. P. (1957): *The Practitioner*, **179**, 378.
Henderson, P. (1961): Personal communication.
Hubble, D. (1959): *The Practitioner*, **183**, 411.
Hutchison, R. (1953): *Brit. med. J.*, **i**, 671.
Illingworth, R. S. (1960): 'The Development of the Infant and Young Child: Normal and Abnormal', Edinburgh.
——, and Knowelden, J. (1961): *Lancet*, **i**, 877.
Institute of Child Health (1959): Annual Report, London.
Lightwood, R. (1958): *The Practitioner*, **181**, 404.
——, Brimblecombe, F. S. W., Reinhold, J. D. L., Burnard, E. D., and Davis, J. A. (1957): *Lancet*, **i**, 313.
MacLean, D. W. (1955): College of General Practitioners' Research Newsletter No. 11.
Miller, F. J. W., Court, S. D. M., Walton, W. S., and Knox, E. G. (1960): 'Growing Up in Newcastle upon Tyne', London.
——, and McDougall, R. (1954): *Brit. med. J.*, **ii**, 846.
Ministry of Education (1960): 'The Health of the School Child. Report of the Chief Medical Officer for 1958-59', H.M. Stationery Office, London.
Ministry of Health (1959): 'Report of the Maternity Services Committee', H.M. Stationery Office, London.
Ministry of Health and Central Health Services Council (1959): 'The Welfare of Children in Hospital', H.M. Stationery Office, London.
—— (1961): 'The Prevention of Prematurity and the Care of the Premature Infant', H.M. Stationery Office, London.
Neale, A. V. (1961): *J. Coll. gen. Pract.*, **4**, 19.
Platt, R., *et al.* (1957): *Lancet*, **ii**, 510.
Roberts, L. (1953): *Brit. med. J.*, **ii**, 962.
Schaffer, A. J. (1960): 'Diseases of the Newborn', London.
Schlesinger, B. (1955): *Gt Ormond Str. J.*, **9**, 2.
—— (1960): *The Practitioner*, **185**, 426.
Scott, R. (1961): Personal communication.
Sheridan, M. D. (1960): 'Developmental Progress of Infants and Young Children', H.M. Stationery Office, London.
Smellie, J. M. (1956a): *The Practitioner*, **177**, 397.
—— (1956b): *Brit. med. J.*, **i**, Supplement, p. 256.
Spence, J., and Court, D. (1950): *Ibid.*, **ii**, 920.
——, Walton, W. S., Miller, F. J. W., and Court, S. D. M. (1954): 'A Thousand Families in Newcastle upon Tyne', London.
Sykes, C. G. W. (1961): Personal communication.
Taylor, M., and Davidson, A. (1959): *Lancet*, **ii**, 453.
Thomson, W. A. R. (1960) *J. Roy. Inst. publ. Hlth*, **23**, 290.
von Reuss, A. (1920): 'The Diseases of the Newborn', London.
Warin, J. F. (1959): In 'Recent Advances in Public Health', 2nd ed., edited by J. L. Burn, London, p. 42.
Watson, G. I. (1955): *Brit. med. J.*, **i**, 5.
Watts, C. A. H. (1960): *Ibid.*, **ii**, 416.
Westmacott, I. (1961): Case Conference No. 7, p. 169.
Wofinden, R. C. (1960): 'Report of the Annual Conference of the National Association for Maternal and Child Welfare', London.

ADVANCES IN THE TREATMENT OF SKIN DISEASES

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Dermatological nomenclature has for long been a source of innocent merriment to other doctors, and indeed it is a curious fact that the skin can be afflicted by so many diverse lesions. It should be realized, however, that over ninety per cent. of all dermatoses are due to a small group of common skin conditions: i.e. such diseases as eczema-dermatitis, warts, acne vulgaris, rosacea, psoriasis, alopecia areata, urticaria and fungus infections. The

Year	Number of cases		
	New outpatients	Eczema-dermatitis	Warts
1946	6,456	2,088	662
1950	6,623	1,904	1,367
1955	7,773	1,991	2,299
1960	9,154	1,527	3,785

Table I.—Incidence of the eczema-dermatitis group and of warts in the Skin Department, Royal Infirmary, Edinburgh, 1946-60.

preponderance of some common diseases is shown in table I, based upon the records of the Skin Department, Royal Infirmary, Edinburgh.

As in other branches of medicine, many common ailments have not been conquered by recent therapeutic discoveries and the main advances have been made in the elucidation and treatment of the more exotic eruptions, which possibly interest the dermatologist more than the family doctor.

LOCAL CORTICOSTEROIDS

These potent two-edged weapons are being used more and more in different skin diseases, and fortunately when prescribed as local applications are little liable to cause adverse reactions. It is possible that much suffering and misery have been relieved by the judicious use of these expensive preparations, which are best applied in the form of ointments and lotions, for elegant cream bases may produce a contact dermatitis and the sprays at present so popular are wasteful and inefficient: a careless patient may expend 100 ml. in a single application. Hydrocortisone and prednisolone ointments and lotions still have an important place, but are being superseded to some extent by triamcinolone which, in the form of triamcinolone acetonide ointment (0.1 per cent.), in controlled experiments by various authors, such as

Crowe and his colleagues (1958), Vickers and Tighe (1960) and Polano (1961) has proved to be more effective than the older drugs. In many cases of non-infective eczema triamcinolone ointment has a much more potent therapeutic effect, but it must be remembered that it is more expensive.

A new synthetic corticosteroid, fluocinolone acetonide, was used by Robinson (1961) in double-blind studies in the treatment of dermatoses usually responsive to local steroid treatment. He found a preparation containing 0.025 per cent. fluocinolone acetonide to be at least as effective as one containing 0.1 per cent. triamcinolone acetonide and definitely superior to one containing 1 per cent. hydrocortisone. Clinical trials of this new steroid are at present being carried out at several centres in this country with similar results, and it is possible that, when generally available, it will be less expensive than triamcinolone acetonide.

The gradual fall in the incidence of the eczema-dermatitis group since 1955 (table I) may indicate that fewer patients with eczema have to be referred for specialist advice because of the efficacy of corticosteroids applied by the family doctor.

INTRA-LESIONAL CORTICOSTEROIDS

The intra-lesional injection of corticosteroids is becoming popular in strictly localized dermatoses, and here again the effect of triamcinolone seems to be superior to the others. Such injections may produce a most satisfactory result in isolated patches of alopecia areata, e.g. of the eyebrows, as shown by Berger (1961); lichen simplex chronicus; psoriasis; hypertrophic lichen planus; keloid; granuloma annulare; and even discoid lupus erythematosus and sarcoidosis. Information regarding this method can be obtained from the articles written by Cohen and Baer (1960), Pelzig and Baer (1960), and James (1960).

SYSTEMIC CORTICOSTEROIDS

Systemic corticosteroids should be prescribed for dermatological conditions only after consideration of the patient from all viewpoints, bearing in mind the remark of a rheumatologist: 'I have often regretted putting a patient on steroids, but have never yet regretted not doing so'. Indications can be divided into three categories:—

(i) *Potentially fatal dermatoses* such as the pemphigus group, disseminated lupus erythematosus, dermatomyositis, and exfoliative dermatitis, including the reticuloses.
(ii) *Acute self-limiting dermatoses* such as drug eruptions, erythema multiforme, giant urticaria, severe contact dermatitis, and papular lichen planus.
(iii) *Chronic dermatoses* such as severe asthma-eczema, alopecia totalis and psoriasis, in which all other possible treatments have failed. In other words this indication is a rare one.

Except for psoriasis, in which triamcinolone is by far the most effective, the response to a steroid in these diseases is unpredictable. One patient may respond to cortisone, one precisely similar to prednisolone, and yet another to corticotrophin, and for this and other reasons it is wiser to treat these

patients in hospital until the most suitable drug and the optimum dosage can be determined. For those on long-term therapy and not to be trusted to adhere to their scheduled oral dose, Alexander and Harvey (1960) recommend a long-acting intramuscular preparation of methylprednisolone acetate which also seems less liable to cause gastric reactions. One of the new corticosteroids, betamethasone, is not only the least costly of these drugs, but is claimed to have other advantages such as no tendency to cause œdema or muscle weakening. In my limited experience of this drug, these claims have so far been substantiated, but in a pilot trial of this drug in 30 patients Wilkinson (1961) concluded that betamethasone, 0.5 mg., is slightly more effective than dexamethasone, 0.5 mg., and equivalent to, or slightly better than, prednisolone, 5 mg., in the 14 patients in whom they were compared, and that dyspepsia was infrequent. Moon-face appeared in half those treated.

Anabolic steroids have little place in dermatology, but may be of value in some cases of disseminated lupus erythematosus and acrodermatitis perstans and may be indicated for patients on prolonged corticosteroid therapy.

ANTIBIOTICS AND ANTISEPTICS

Antibiotics by mouth or by injection are seldom required for skin diseases, and the indications depend upon the type of disease and the relative resistance of the responsible organisms. If possible, they should be withheld in such conditions as recurrent furunculosis, in which drugs such as penicillin make the patient even more liable to further attacks, whilst resistant strains of staphylococci may be produced. The dermatologist regards streptomycin and penicillin as the two most apt to cause cutaneous reactions: penicillin is now the commonest cause of giant urticaria. In a series of 300 patients with urticaria, in 14 per cent. the rash was precipitated by parenteral penicillin.

Penicillinase has been advocated in the treatment of penicillin urticaria. In a few cases my own experience has been decidedly disappointing, and does not confirm the results obtained by Becker (1958,1960).

Griseofulvin has proved its worth in ringworm infections, but only too often it is prescribed for diseases not due to tinea: e.g. perionychia caused by *Candida albicans*. It is therefore advisable to establish the diagnosis by microscopic and cultural examination before using the drug. In acute and mild fungus infections, griseofulvin is often effective when given in a short course for three or four weeks, but in chronic cases, especially with involvement of the nails, it must be continued for many months. Finger-nails can often be cured in four or five months, but toe-nails may be still infected after a year's constant therapy, even combined with surgical removal. The results obtained in the Skin Department, Royal Infirmary, Edinburgh, in 1959-1960 are shown in table II.

Local antibiotic therapy is often used in pyogenic infections with a tendency to employ the tetracycline series less and less, and to prescribe instead antibiotics seldom given parenterally. Of the latter, neomycin is

possibly the most popular, but in some ways it is not as effective as framycetin, which rarely causes reactions and is speedily effective in diseases such as impetigo circinata. Many antibiotic ointments and lotions are now combined with one of the steroid drugs.

Local antiseptic therapy is tending to oust the antibiotic-steroid applications, and of these the most useful are the quinoline group such as 'compound quinolor ointment', 'vioform cream' and 'steroxin ointment', which may also be used combined with corticosteroids. They have the advantage that antibiotic-resistant strains of organisms are not produced, and that

	Cured	Improved	Unchanged	Stopped treatment
Finger-nails				
1959	21	—	1	2
1960	13	7	1	—
Total	34	7	2	2
Toe-nails				
1959	14	11	1	4
1960	8	20	1	—
Total	22	31	2	4

TABLE II.—Cases of tinea unguium treated in the Skin Department, Royal Infirmary, Edinburgh, with griseofulvin, and assessed in December 1960.

they are fungicides, so that yeast infections do not flourish in place of the pyogenic bacteria. Antiseptics which are particularly valuable in exudative flexural eczema and in pruritus ani are domiphen bromide and dequalinium chloride, applied in 3 per cent. strength in a steroid ointment.

LEG ULCERS

Before treatment is instituted for a leg ulcer, it is important to be sure of its causation. Many patients are diagnosed as having 'varicose ulcers' although they have never had a varicose vein in their lives. A better term is 'stasis ulcer', as it is often the deep veins which have thrombosed. In recent months I have seen tuberculous ulcers, gummas and leishmaniasis, which have been treated for months as 'varicose ulcers' before the real cause was detected. It is advisable also not to forget that the patient's ulcers may be trophic ones associated with nervous or vascular disease, or even artefacts in hysterics or malingerers.

Although local antibiotic therapy is popular, it has little to commend it, and Fergusson and Logan (1961) performed a useful service when they clearly demonstrated in a large series of cases that eusol is still the most effective application, used as a wet dressing. This must, of course, be supplemented by complete bed rest or a suitable supporting bandage. Once the ulcer has healed, the Bisgaard technique—regular massage, the use of padding over hollows and the ulcer itself, and efficient elastic bandage

—helps to prevent relapse. Modern crêpe bandages have little to commend them, as they have almost no elasticity and tend to cut into the skin.

If a stasis eczema is present, it should be treated as a low-grade infective eczema with appropriate dressings, such as 0.5 per cent. silver nitrate soaks with a waterproof backing until the area is well tanned. Then 'vioform cream', 1.5 per cent., Lassar's paste spreads, or, in some cases, crude coal tar can be prescribed.

ACNE VULGARIS

Really effective therapy has not yet been achieved for acne vulgaris, and its associated oily seborrhœa. Patients with Parkinsonism not infrequently are affected by seborrhœa oleosa, and Gillingham (1960) has observed that the skin of some may return to normal following the intracranial operation. This interesting finding opens a wide field for speculation and research. Endocrine treatment has on the whole been decidedly disappointing, although the acne of some girls responds reasonably well to the administration of œstrogens; most, however, do not. Some improve considerably with the application of an epiœstriol cream such as 'actriol', but by no means all. Probably local applications which produce adequate desquamation are still as efficient as any. A modern abrasive cream such as 'brasivol' can be used in varying strengths, as recommended by Saperstein (1960). I have used these creams since 1958 with good effect and Alexander and Vickers (1961) also recommend them. A highly effective ointment which has stood the test of time is the Vienna peeling paste:—

Betanaphthol B.P. 1948	10.0 g.
Sublimed sulphur	50.0 g.
Soft soap	25.0 g.
Soft paraffin	25.0 g.

This can either be applied as a spread removed after twelve hours, or rubbed in for three successive nights or until a brisk exfoliation occurs. The treatment is repeated when the skin has recovered: i.e. in approximately ten days.

For a number of years vitamin A in a dosage varying from 50,000 to 150,000 units daily has been advocated, and this treatment sometimes appears to be effective, especially in acne patients with a tendency to follicular hyperkeratosis. As with so many drugs, its value has not been assessed accurately by a controlled series of cases, but this may soon be forthcoming.

SEDATIVES AND TRANQUILLIZERS

In many skin conditions such as eczema, alopecia areata and lichen planus, some form of sedation is often indicated. Hopes that at least one of the many tranquillizing drugs now available would be effective in these dermatoses have not been fulfilled. For example, in a double-blind controlled pilot trial, we found that the effects of the placebo were almost as good as those of three tranquillizing drugs of dissimilar chemical structure, and had no side-effects such as drowsiness (Peterkin *et al.*, 1961). For night-time sedation, thalidomide, 100 to 200 mg., or dichloralphenazone, 150 to 300

mg., is useful, and a small dose of phenobarbitone for day-time use is still as effective as any other drug. Although their sedative effect is excellent, preparations containing carbromal, such as 'carbrital', are not prescribed by dermatologists because of the characteristic purpura often produced by this drug. Whilst the antihistamines are indicated in urticarial eruptions, they have little effect in controlling pruritus in other diseases, but their sedative action is not to be despised, and they are often employed for this reason.

DIFFUSE HAIR LOSS IN WOMEN

In many countries during the past five years, dermatologists such as Sulzberger, Witten and Kopf (1960) have been consulted by an increasing number of women affected by a diffuse loss of scalp hair, apart from those with endocrine disturbances such as myxœdema. Various reasons for this have been suggested, two of these being locally applied chemical substances and the ingestion of certain drugs. 'Cold wave perms', dyes, bleaches (which sometimes contain ammonium persulphate), shampoos and lacquer may all have a deleterious effect on the hair keratin, whilst nylon brushes, as Agnes Savill (1958) showed, may cause shredding of fine hair. It is little wonder that Nature at last revolts! Some years ago, in Sweden, England and the United States, it was observed that some cardiac patients on drugs such as heparin and dicoumarol developed a diffuse alopecia. In recent months I have seen two women who lost much of their hair while on the tranquillizer, trifluoperazine, and whose hair re-grew when the drug was stopped. The powerful cytostatic drugs prescribed for certain malignant diseases can have a similar action. For example, in a series of 25 patients treated with cyclophosphamide Falkson and Schulz (1960) noticed that ten of them developed an alopecia.

Vitiligo may occur in association with alopecia areata, and these leucodermatous patches are distressing to patients, especially if they appear on exposed parts. No effective therapy has yet been discovered for this disease, as treatment with the extract of the plant *Ammius majus* ('meladinine') has been disappointing. It is possible, however, to give a patient an artificial 'sun-tan' by means of dihydroxyacetone, which is a harmless three-carbon sugar. When it is applied to a depigmented area, a non-melanin pigmentation appears, and with care an intelligent individual can disguise his lack of pigment, as has been pointed out by Mumford (1960), Blau and his colleagues (1960) and Maibach and Kligman (1960). A warning must be given that this type of tan does not prevent the sunburn to which these people are particularly liable.

TUMOURS OF THE SKIN

Warts are becoming much more prevalent, and are tending to be more resistant to treatment. Nevertheless, successes are often obtained by simple methods, such as 'elastoplast' dressings left on for two or three weeks at a time, and continued for six weeks if necessary, or by soaking the warts every night in a 3 to 6 per cent. solution of formalin. For the common wart,

freezing with liquid nitrogen or oxygen is as effective as anything; for the more deep-seated plantar wart curettage can be used or the application of 50 per cent. podophyllin in light liquid paraffin, inserted into the lesion by an orange stick. Intense reactions can occur with these applications, but soon subside with symptomatic remedies.

Basal-cell carcinoma is treated in most hospitals by radiotherapy, the best cosmetic results being obtained when the growth is first removed by

Cause	No. of cases	Cause	No. of cases
Medicaments (Medically prescribed) Antihistamines 15 Antibiotics 8 Antiseptics 8* Other drugs 5†	36	Soap (containing deodorant)	7
Medicaments (Self-prescribed)	10	Cosmetics 'Cold perms' 6 Hair dye 3 (Other causes included face cream, face lotion, shampoo, hair lacquer, deodorant, suntan lotion, setting lotion, hand cream, nail varnish, and talcum powder)	22
White metals Nickel (e.g. suspender clips) 17 Chrome 5	22	Plants (Of which 10 due to primula obconica)	13
Rubber e.g. Gloves, shoes, helmet lining	11	Various causes (Lavatory seats, teak, turpentine, carbon tetrachloride, cycle cleaner, fertilizer, spectacle frames and orange crush)	9
Garments e.g. Dye from dresses, shirts	19	Undiscovered	29

* Four due to ammoniated mercury. † Two due to local anæsthetics.

TABLE III.—Analysis of causes of contact dermatitis, seen in the Skin Department, Royal Infirmary, Edinburgh, during 1960.

thorough curettage, followed by x-rays later. With this method a smaller dosage of x-rays is required, and there is little risk of a trophic ulcer occurring some years afterwards. Surgical removal is the treatment of choice for rodent ulcers whose situation allows of a wide excision, and for most cases of multicentric basal-cell carcinoma. In recent years, it has been demonstrated that sometimes this form of carcinoma can be cured by the application of drugs such as colchicine and podophyllin, and more recently Van Scott and his colleagues (1960) treated seven patients orally with the folic acid antagonist, methotrexate. Although complete cure of all the tumours was not achieved, most of them were reduced in size, and a few vanished. This experimental work envisages the possibility that at some future date such growths will be routinely treated by oral medication.

Malignant melanoma, despite its grave significance, has not an entirely hopeless prognosis. Recent follow-up surveys have revealed a surprisingly high survival rate following radical surgical measures. For instance,

Buchanan (1961) in a series of 26 patients had a five-year survival rate of 69.6 per cent. but, as he is careful to emphasize, this is not tantamount to a cure. Fresh hope for these victims has been provided by the work of Ryan and his colleagues (Creech *et al.*, 1959), who have treated many patients with malignant melanoma using an isolation-perfusion technique. This allows of a high local concentration of a drug such as phenylalanine mustard to be given to an area such as a limb with the minimum of systemic effect. I have seen the results in some of these cases, and they are extremely impressive, but time must elapse before a final assessment can be made.

CONTACT DERMATITIS

An analysis of patients with contact dermatitis seen during 1960 produced some interesting information (table III): 183 cases were seen, of which 113 were women. Prescribed medicaments accounted for 36, including 15 caused by antihistamine ointments and lotions which dermatologists never prescribe because of their sensitizing potential.

CONCLUSION

A great deal of progress has been made in dermatology during the last decade, but there is still much to be done. Let us always remember that 'wonder drugs' such as corticosteroids and antibiotics may not only save lives and relieve misery, but may also have precisely the opposite effect, and therefore must be prescribed for sound reasons and after due deliberation.

References

Alexander, J. O'D., and Harvey, G. (1960): *Lancet*, **ii**, 437.
Alexander, S., and Vickers, H. R. (1961): *The Practitioner*, **186**, 92.
Becker, R. M. (1958): *Ann. intern. Med.*, **48**, 1228.
—— (1960): *The Practitioner*, **184**, 447.
Berger, R. A. (1961): *A.M.A. Arch. Derm.*, **83**, 151.
Blau, S., Kanof, N. B., and Simonson, L. (1960): *Ibid.*, **82**, 501.
Buchanan, R. N. (1961): *Ibid.*, **83**, 447.
Cohen, H. J., and Baer, R. L. (1960): *J. invest. Derm.*, **34**, 271.
Creech, O., Ryan, R. F., and Krementz, E. T. (1959): *J. Amer. med. Ass.*, **169**, 339.
Crowe, F. W., *et al.* (1958): *J. invest. Derm.*, **31**, 297.
Falkson, G., and Schulz, E. J. (1960): *Brit. J. Derm.*, **72**, 296.
Fergusson, A. G., and Logan, J. C. P. (1961): *Brit. med. J.*, **i**, 871.
Gillingham, F. J. (1960): Personal communication.
James, A. P. R. (1960): *Antibiot. Med.*, **7**, 495.
Maibach, H. I., and Kligman, A. M. (1960): *A.M.A. Arch. Derm.*, **82**, 505.
Mumford, P. B. (1960): *Brit. J. Derm.*, **72**, 279.
Pelzig, A., and Baer, R. L. (1960): *J. Amer. med. Ass.*, **173**, 898.
Peterkin, G. A. G., *et al.* (1961): Unpublished data.
Polano, M. K. (1961): *A.M.A. Arch. Derm.*, **83**, 214.
Robinson, H. M., Jr. (1961): *Ibid.*, **83**, 149.
Saperstein, R. B. (1960): *A.M.A. Arch. Derm.*, **81**, 601.
Savill, A. (1958): *Brit. J. Derm.*, **70**, 296.
Sulzberger, M. B., *et al.* (1960): *A.M.A. Arch. Derm.*, **81**, 556.
Van Scott, E. J., *et al.* (1960): *Ibid.*, **82**, 762.
Vickers, C. F. H., and Tighe, S. M. (1960): *Brit. J. Derm.*, **72**, 352.
Wilkinson, D. S. (1961): *Brit. med. J.*, **i**, 1319.

ADVANCES IN CARDIOLOGY

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ADVANCES which most interest the practitioner are those which he himself can use in his practice. Those which can only be used in hospital must interest him less, and hospitals are often at fault in detaching the patient from his doctor, who still has to accept the day-to-day responsibility. Nevertheless, the latter should know what can be achieved in hospitals or in special centres so that he can be assured that his patients are all covered by medical progress, and that they do not feel they are missing something which comes their way by gossip, the Press, or fireside entertainment. With a literature of epoch-making discoveries and easy therapy cascading through the letter-box it is difficult to know what is reasonable and practical and it is important to realize that increased knowledge of disease which leads to better management and advice may be more helpful than new treatments. These may also prove a mixed blessing to the patient and it would be possible to write entirely on 'Disadvantages of Advances'. All these points have influenced both the selection and discussion in this article.

HYPERTENSION

Since the last article on 'Advances in Cardiology' (Gavey, 1957), two new groups of hypotensive drugs have been used: the oral diuretics of the chlorothiazide group and the sympathetic blockers. Which patient to treat and at what stage of the disease are still difficult decisions for, as there are few who feel better when their pressure is lowered with drugs, it is important to know that they are better and that their future is materially altered. Treatment which is too vigorous, or applied with too rigid a zeal in maintaining low sphygmomanometer readings may do more harm than good. Care is particularly needed in the old and in those who may have stenosis of carotid and vertebral arteries, for an abrupt fall of blood pressure may precipitate a stroke. Availability of treatment does not obviate the need for searching for a cause, particularly in younger patients without a hypertensive family history. A long follow-up by Sokolow and Perloff (1961) has shown that mild hypertension is often far from 'benign', which emphasizes the importance of advances in control of the disease and observation of patients so that they can be treated early if disease is progressive.

The oral diuretics have a definite but limited effect in lowering pressure. Their mode of action is not precisely known but a diminished blood volume is one factor, and by their use the dose and thereby the side-effects of ganglion- or adrenergic-blocking drugs may be reduced. In hypertensive heart failure their value is not, of course, confined to the hypotensive effect but they should not displace digitalis.

The undoubted effectiveness of the drugs which acted by blocking

autonomic ganglia was limited by unpleasant, often intolerable, and sometimes dangerous parasympathetic side-effects, so that the introduction of drugs with a specific action on the sympathetic nervous system was a welcome advance. Bretylium tosylate was first used in 1959 and preliminary trials in hospital were encouraging, but irregular and unpredictable action, hypotension on exercise, and the development of tolerance proved to be severe practical disadvantages, and it was not free from side-effects. Guanethidine, though chemically unrelated, has a similar selective action on sympathetic tone. It arrived in this country in 1959 although the first reports were in the American literature two years before. The first English report (Leishman, Matthews, and Smith, 1959) showed a more sustained and predictable effect than bretylium, which was confirmed by other early trials (Dollery, Emslie-Smith and Milne, 1960) and recently by the original authors (Leishman *et al.*, 1961) after a further experience of twenty months. It is now the drug of choice for severe hypertension. Only one daily dose by mouth is needed and its sustained effect makes it possible by weekly increments of 10 mg. to achieve control without hospital admission, although this is advisable with older patients or in advanced disease when smooth initial control is vital. Blood-pressure readings must be recorded standing because of its postural effect, and postural faintness may occur, particularly in the early morning. Syncope on exertion due to a marked fall in peripheral resistance is rare, in marked contrast to bretylium which had the additional disadvantage of causing a rise in pulmonary resistance (Taylor and Donald, 1960). Drug tolerance occurs in only 20 per cent. and usually requires only one small increase of dose. This must not be confused with loss of control associated with abrupt weight increase due to fluid retention, a side-effect which may be mistaken for heart failure. Increase of guanethidine dosage is contraindicated and the situation is restored without reduction of the dose by a brief course of diuretic therapy (Leishman *et al.*, 1961). Other side-effects occur. Diarrhœa is common but not severe and will respond to codeine, kaolin, anticholinergic drugs or pempidine tartrate. Muscle pain and weakness, exertional dyspnœa, bradycardia which may be accentuated by digitalis, failure of ejaculation, and depression, are additional disadvantages but they are mild compared with the side-effects of the ganglion-blocking drugs. Although the side-effects of guanethidine may limit treatment they rarely cause it to be abandoned and most patients appreciate the change to this drug.

There is still a place for ganglion-blocking drugs, particularly mecamylamine and pempidine, for those already under satisfactory control by them and for the patient with severe disease who does not respond to guanethidine. Closer supervision is needed both for the troublesome side-effects and for adjustment of dosage: these are exacting problems for the busy practitioner and, as it is only the severest cases who should be subjected to their disadvantages, there is much to be said for hospital control.

Reserpine is still valuable either in controlling the mild, hyperdynamic,

hypertensive or in combination with the more active hypotensive agents in severe cases. Reserpine has a central action on the hypothalamus but probably a direct action on peripheral vessels as well. Its main disadvantage is depression and the patient should be told to report the first sign of this, for not only may this progress to a suicidal stage but more commonly he continues as a misery not only to himself but to those who live with him, and assumes that this is due to his disease and not the treatment.

CORONARY ARTERY DISEASE

Epidemiological studies have stressed the importance of two factors in the etiology of coronary artery disease—too little activity and too much of too rich a diet—and both have influenced treatment. In a disease in which acute exacerbations are a characteristic feature periods of rest are clearly indicated, but it is now recognized that in the intervals reasonable physical activity is to be encouraged. In the treatment of acute infarction the strictness and the duration of bed rest have been lessened and tempered to the severity of the attack with no added danger and much improvement to the spirits of most patients. Obesity, particularly if we include all patients in whom the caloric intake is too high for the degree of physical activity, not only increases the incapacity caused by coronary artery disease but in addition few could now deny that it is an important factor in causation.

A high-fat intake, or alimentary lipæmia, may not only encourage thrombosis in susceptible individuals but the implication of animal fats and saturated fatty acids in the formation of atheroma has become increasingly convincing. The evidence is no longer confined to animal experiments or merely circumstantial. Unfortunately there is no close correlation between the level of cholesterol in the blood and clinical disease, and it is common to find patients with evidence of widespread atheroma with a normal blood cholesterol. This is relevant to cholesterol-lowering treatments with low-fat diets, unsaturated fatty acids, œstrogens, thyroid compounds, nicotinic acid, sitosterol, or the most recent agent, triparanol, a sterol which interferes with the synthesis of cholesterol, for an alteration in cholesterol metabolism does not necessarily mean a reduction in deposits in the vessels. The laboratory and animal work on triparanol is impressive and it has been shown to lower the blood cholesterol in man, but the clinical evidence that it has a beneficial effect on disease is not convincing (Proceedings of the Conference on MER 29, 1960), nor has one heard so far any favourable reports from those who have investigated its use in this country. Nevertheless, the manufacturers can be congratulated both for undertaking the research work to produce an agent which has added to knowledge, and for organizing early publication of experimental and clinical evidence as a guide to those who are invited to use it in practice.

The etiological problem of atheroma is, of course, a more complex one than can be assessed by the blood level of cholesterol alone. The quantity and quality of research now being done may make it possible to prevent

or control disease by taking anti-atheromatous substances or by a prophylactic diet, but the position is not yet clear enough to advise this except in selected patients. When atheroma is severe it may well be too late, but it is reasonable to counsel restriction of animal fats for those who will appreciate every possible protection and will keep to it, and also with the early manifestation of disease, particularly when family history, constitution and way of life would indicate increased susceptibility. The use of vegetable fats makes for a more reasonable diet but it must be made clear that it is the replacement of animal fats that is likely to confer protection and a total fat intake of 25 per cent. to 30 per cent. of total calories with a ratio of 3 to 1 vegetable to animal fat should be the aim. The patient must not only be informed, but willing to submit to dietetic control. Some are not, as was well expressed by a fat and jolly man after a large dinner: 'They say that thin men live longer, but perhaps it may seem longer'.

ANGINA PECTORIS

Glyceryl trinitrate is still the most valuable drug in angina and by its intelligent use the patient with chronic angina is helped to lead a reasonable life. Not only does it relieve pain but it has been shown to improve the efficiency of the left ventricle (Müller and Rǿrvik, 1958). Very few patients cannot tolerate it and its only disadvantage is the short duration of its action. The search for a long-acting nitrite is therefore understandable and praiseworthy but so far no reliable drug has been found which has proved itself either in practice or clinical trials. Because of the claims that have been made for long-acting preparations it is not uncommon for patients to be denied the drug of proven value, and until a satisfactory long-acting preparation is found it is surely logical to use glyceryl trinitrate more freely for relief and prevention of pain. Alternative drugs to the nitrites have also been unsatisfactory. Khellin had its day and, whilst Towers and Wood (1958) found iproniazid helpful, it had limiting side-effects. Since then other mono-amide oxidase inhibitors without side-effects have been produced but have not been shown to be effective.

Even if a drug were found which would prevent angina completely it could have potential danger, for the sudden development, exacerbation, or alteration in the type of angina may indicate progression of coronary artery disease requiring treatment in addition to a pain-abolishing drug. Such a warning indicates the need for a period of rest and the trend of opinion is strongly veering to the use of anticoagulants for such episodes. With an electrocardiogram showing ischæmic changes, without conclusive evidence of an infarction electrocardiographically or clinically, the prophylactic use of anticoagulants is strongly indicated.

Chronic angina is sometimes due to inadequate treatment when fear is uncontrolled, general measures are forgotten, and drug therapy is not properly used, and some of these patients are included in reports on surgical treatment for 'intractable' angina. Surgery for relief of angina has a

place, however, and bilateral upper dorsal sympathectomy may improve myocardial function quite apart from relief of pain (Hayward, 1961). The future of cardiac surgery would appear to lie in coronary endarterectomy in selected cases of angina. Crawford and his colleagues (1961) demonstrated in careful pathological studies that in 9 of 75 cases coronary atheroma was remarkably localized. Coronary angiography is developing so that it is possible to demonstrate such localization. By careful correlation of pathological and radiological evidence with the clinical course and patterns of coronary artery disease it should be possible to discover in which patients the lesion is so localized that obstruction may be removed, for coronary endarterectomy has already been successful.

TREATMENT OF ACUTE MYOCARDIAL INFARCTION

The rapid action of heparin, as compared with the oral anticoagulants, determines its use in the first few hours of the acute attack of myocardial infarction. Although there is little evidence that it prevents extension of thrombosis, the prompt relief of severe and prolonged pain that sometimes occurs is suggestive and impressive. The rapid action is not without its dangers, however, particularly in the elderly with cerebral atheroma, and its use is best confined to those treated in hospital or who are being admitted to hospital. In profound shock a noradrenaline drip is of proved value but when this is not possible metaraminol, 5 to 10 mg. intramuscularly, will raise the blood pressure in a few minutes and the effect will last for up to forty minutes. The dangers of digitalis after infarction have been too much stressed and in the early stages it is indicated intravenously for shock or left ventricular failure, and later if congestive failure develops or atrial fibrillation persists.

ANTICOAGULANT THERAPY

All are now agreed on the efficacy of anticoagulant therapy in prevention and treatment of venous thrombosis and consequent pulmonary embolism. Less can be expected from anticoagulants in atheromatous arteries for there is the additional factor of disease of the vessel wall and narrowing of the lumen. The lowered mortality from myocardial infarction when anticoagulant therapy is well controlled in hospital is generally accepted but this is mainly due to fewer thrombo-embolic complications rather than prevention of further thrombosis in the diseased coronary arteries. Knowledge of what this group of drugs can be expected to achieve, to which patients they should be given and of the complex mechanisms involved and the difficulties of adequate control, has advanced considerably. Both are important, for the prophylactic, now added to therapeutic, treatment poses problems of organization, staffing, and expense on a national scale.

In coronary artery disease there are few who would withhold this therapy for acute myocardial infarction except possibly for 'mild-risk' cases, though these are not always predictable, or when there are definite contraindications, or advanced age. Most would agree that effective and safe control can rarely

be achieved outside hospital, and the need for anticoagulant therapy should therefore be a major factor in deciding whether to treat the episode at home or in hospital. Prophylactic and long-term treatment is a more difficult problem. Two trials of long-term therapy after infarction have produced evidence on which some reasonable policy can for the present be adopted —those of Bjerkelund (1957) and of the Medical Research Council (1959)— and both suggested that anticoagulants could be beneficial. Following the recommendations of the M.R.C. trial, those who dislike anticoagulants— and many have reason to distrust them from experience of isolated patients —were encouraged by the scepticism of McMichael and Parry (1960) of long-term therapy. Their report was valuable in once again emphasizing that the prognosis after infarction is not as gloomy as the patient and his relations often think, but it has been criticized for being as biased as some of the reports it attacked.

Owren (1961), acknowledged as an expert in anticoagulant control as well as a clinician of sound judgment, has reported favourably on their prophylactic use in angina, and Wood (1961) has produced convincing evidence of their value in acute coronary insufficiency as manifested by exacerbations of angina, atypical angina, and angina at rest. In patients with peripheral vascular disease the high subsequent incidence of coronary and cerebral episodes (Boyd, 1960) indicates a further group in whom prophylactic treatment should be considered.

In the difficult decision of anticoagulant treatment more evidence will certainly come and will be welcome, but it would seem reasonable on present evidence to consider it for males under 55 with a recent myocardial infarction, and to continue it for at least one year; as prophylactic treatment in acute or subacute coronary insufficiency; and in younger patients with angina and peripheral vascular disease. In preventive treatment it is clearly better to use it early rather than late in the disease and the individual decision to treat should embrace every factor and will undoubtedly be influenced by the philosophy of the doctor himself. The most important points are whether the patient can accept the inconvenience of ambulant therapy imposed by the absolute necessity for good control, and whether this is available, for otherwise it is a dangerous placebo.

Much has been learnt about the mode of action of the anticoagulants but as at least four factors in blood clotting are involved it is not surprising that there is no general agreement about levels of control, no simple test to ensure control, and even that results are expressed differently. With Quick's one-stage test, prothrombin times vary with the thromboplastin used and it is safest to report both control time and patients' time in seconds and then the ratio of the two: e.g. control 12 seconds, patient 30 seconds, ratio 2.5. A ratio of between 2 and 7.5 is the generally accepted aim. Owren's (1959) 'thrombotest' has gained some support in this country; although more expensive it saves in technicians' time and has some theoretical advantage, but Quick's test is still the most widely used here. The essence of

good control is unremitting care and with this disasters from bleeding are increasingly rare. With so many factors affecting control the patient should carry a card on which the current dosage is written and also instructions to ensure reasonable care. One person must be responsible for the dosage, and as this may be difficult for the consultant or practitioner in charge, there is much to be said for the person who does the test prescribing, provided essential liaison is maintained.

Coincident with work on anticoagulants the mechanisms of fibrinolytic activity have been studied with a view to treatment. The technical difficulties are great and laboratory control is more complicated and elaborate than with the anticoagulants, but it is right that this logical approach of harnessing a physiological agent should be followed, for practical therapy may result.

EXTERNAL CARDIAC MASSAGE IN CIRCULATORY ARREST

Sudden death may occur from asystole or ventricular fibrillation in patients who are not moribund or doomed to die and may be averted by cardiac massage. Prompt action is needed for unless the circulation is resumed within three minutes irreversible cerebral damage may occur. Until recently this has meant opening the chest and directly compressing the heart between the hands, and such a dramatic procedure has only been possible, or proper, in a hospital. Cardiac arrest may not only occur in the theatre or anæsthetic room, but also in the surgical ward after an operation, or in the medical wards, outpatient and casualty departments, particularly in association with myocardial infarction. It is therefore an emergency which a hospital must be prepared to deal with, and this requires forethought and planning if, in the event, a distressing scene resembling a shambles is to be avoided. Furthermore the heavy responsibility of the quick decision whether to open the chest or not must often rest with relatively inexperienced house officers. The potential danger to epileptics, those likely to faint, or the aged with Stokes-Adams attacks, from knife-happy young residents is obvious. Recent work at the Johns Hopkins Hospital, Baltimore (Kouwenhoven *et al.*, 1961), on reactivation of the arrested heart by external cardiac massage through the chest wall is therefore timely and important. It greatly widens the possibility of saving the occasional life and should be known not only by all doctors, but by first-aid and ambulance workers also.

Preliminary work on dogs had shown that the circulation could be maintained by rhythmic pressure on the chest when the ventricles were fibrillating, and that the heart would resume normal rhythm after defibrillation by an electric shock. The Hopkins workers have shown that closed cardiac massage can be used successfully in man, for the mediastinum is fixed and the chest, even of the adult, is sufficiently flexible to allow compression of the dilated heart in standstill or ventricular fibrillation between the sternum and the spine. Rhythmic, intermittent vertical pressure can maintain a sufficient circulation to keep the brain alive and lungs can be oxygenated

by mouth-to-mouth insufflation (fig. 1). From a recent summary I quote their instructions:

'The patient in cardiac arrest should be placed in a supine position, preferably on a firm support such as the floor, a table or a bed-board. Provide a patent airway by inserting a tube or extending the neck and pulling the jaw up, as in mouth-to-mouth insufflation. Kneel beside the patient and place your hands on the centre of his chest. To find the exact spot, locate the xiphoid and place the heel of the lower hand, with the other hand on top of it, on the sternum just above the xiphoid. Now press vertically downward using the weight of your body, to push the sternum

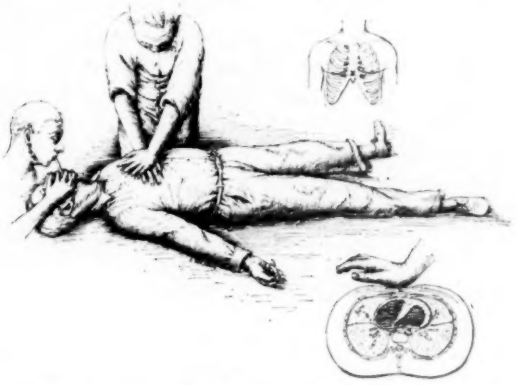

FIG. 1.—Simultaneous application of closed-chest massage and artificial respiration. (After Kouwenhoven, Jude and Knickerbocker, 1961, by kind permission of the American Heart Association, Inc.)

in for a distance of an inch to one-and-one-half inches [25 to 37 mm.]. This action compresses the heart between the sternum and the vertebral column and forces the blood out of the heart and into the lungs and the systemic circulation. Now release the pressure, lifting your hands slightly. This allows the patient's chest to expand fully and the right and left ventricles to refill. Repeat the cycle about 60 to 80 times per minute. If you are the only person present, rapidly ventilate the patient's lungs by giving the patient three or four deep breaths, mouth-to-mouth. Then start massage and, after about a minute or a minute-and-a-half, stop the massage and fill his lungs again with fresh air. If there is someone else present, have him ventilate the lungs simultaneously. There is no need to synchronize the two life-saving procedures'.

They report 68 cases in which 84 attempted resuscitations were made, and in 59 (70 per cent.) a satisfactory return of cardiac and cerebral function was achieved; of 21 resuscitations in operating or recovery rooms all were successful.

When circulatory arrest is due to ventricular fibrillation, and this occurred in 15 of the Hopkins series, a defibrillation shock is necessary to restore normal rhythm. A defibrillator is routinely used in any hospital undertaking cardiac surgery but it is now clearly essential in any hospital where this emergency is to be treated. Defibrillators which can be used with the chest unopened are an obvious advantage, for a situation can arise where the patient is restored to consciousness by external massage and has then

to be given an anæsthetic to open the chest for a defibrillating shock.

Closed cardiac massage is an important advance which should be widely appreciated, for an attempt to maintain the circulation will save some patients with acute myocardial infarction from death, and others may be tided over until a considered decision as to the ultimate prognosis is made.

HEART BLOCK

In 1954, Prinzmetal and Kennamer reported abolition of complete heart block in a patient with acute myocardial infarction by the use of cortisone.

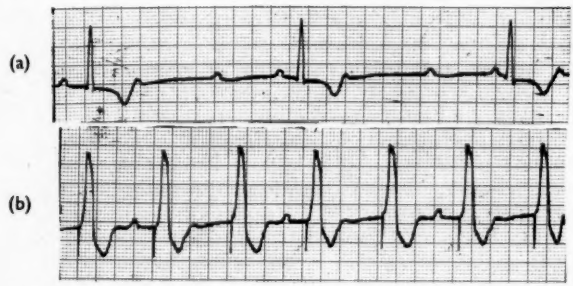

FIG. 2.—(a) Lead 1 of electrocardiogram of female patient of 73 with six months' history of as many as three Stokes-Adams attacks a day, not responding to medical treatment; atrial rate of 80, ventricular rate 28. (b) Electrocardiogram after insertion of artificial pacemaker; ventricular rate 75. The artificial stimulus is seen as a downward deflection immediately before the QRS complex. The patient has had no further Stokes-Adams attacks.

This treatment works by suppressing inflammatory reactions involving the conducting system and is founded upon observations in acute rheumatic carditis, in Addison's disease and in Cushing's disease, and experimental findings in induced myocardial infarction in animals. Experience with this treatment of heart block, both acute with infarction and chronic with Stokes-Adams attacks, has increased and Gilchrist (1960) and Aber and Wyn Jones (1960) have reported favourably upon it. It certainly merits a trial and less salt-retaining steroids than cortisone may be used, particularly when heart failure is present.

Heart block, fortunately usually temporary, occurs in about one-quarter of patients who have surgical closure of ventricular septal defects. In the postoperative period a satisfactory ventricular rate is maintained by regular stimulation from an electrical pacemaker beside the bed through a platinum electrode placed in contact with the heart. This method can be adapted for ambulant patients with Stokes-Adams attacks when conventional drug therapy has failed (fig. 2). Small internal pacemakers can be inserted in the abdominal wall and can have external battery and controls or can be entirely internal. The partially external arrangement has the advantage that the heart rate can be adjusted at will, but has obvious psychological disadvantages. The wholly internal pacemaker will maintain a fixed rate and

the patient is unaware of his life-current, which is advertised to last three years without re-charging; the cost of the device is about £100.

HEART FAILURE

Oral diuretics.—Since Withering discovered digitalis in 1785 there has been no advance in the treatment of heart failure comparable with the oral diuretics. The mercurials had markedly improved the prognosis in many patients with heart failure but the injections necessary limited the use of this therapy and an equally efficient oral diuretic was eagerly sought. None was satisfactory until chlorothiazide, which has been followed by other drugs of the benzthiadiazine group of increased strength and longer action, which were reviewed recently in *The Practitioner* (Morgan, 1961). In the choice of drug there is no virtue in potency for the patient still takes one or two pills and a short-acting intermittent effect is often an advantage as the diuresis is obvious, whereas with the constant use of a longer-acting drug this may not be evident and overdosage may occur. Considering the wide use, toxic effects are rare though they may aggravate or precipitate gout and have caused hepatic coma in liver disease. The oral diuretics have meant that treatment can be given at the earliest evidence of heart failure, which is usually dyspnœa, and in established heart failure they have largely superseded rigid diets and ion-exchange resins designed to eliminate sodium.

Potassium depletion.—A disadvantage of the efficient diuretic is loss of the potassium ion coincident with the desired loss of sodium. Injections did ensure that the patient was seen by the doctor or a visiting nurse but with the oral diuretics he can suffer severe potassium depletion unheeded, particularly if diarrhœa intensifies potassium loss from the bowel. Limp and dehydrated patients with dangerously low potassium levels are not uncommonly seen and may deteriorate or die from uncontrolled treatment. Many patients with small or intermittent dosage may experience malaise, weariness and muscular weakness which is relieved by potassium supplements which are best given on diuretic-free days. Potassium is now added to some preparations but this may not be sufficient to correct depletion and the digitalis intoxication which it causes. As chloride depletion may also occur potassium chloride is the best supplement and although 1-gramme capsules obviate the unpleasant taste of potassium salts these may fail to liberate their contents and the sure way is a mixture which can be stomached by most if strongly flavoured.

Digitalis.—There has been an increasing awareness of the importance of digitalis in heart failure irrespective of its value in controlling atrial fibrillation and other arrhythmias. It is used earlier and is less often discontinued when it has been needed. Despite the success of the oral diuretics in heart failure it must not be forgotten that digitalis acts on the heart and without help in maintaining cardiac output drugs acting on the kidney will be less effective. Unfortunately potassium depletion causes digitalis intolerance and intoxication so that patients may not be able to use the drug they most

need because of diuretics, and this situation occurs more readily as heart failure progresses when the margin between the therapeutic and toxic dose of digitalis narrows. One of the effects of digitalis intoxication is to produce arrhythmias. Mackenzie, in 1911, described atrial tachycardia with a changing heart block resulting from digitalis therapy, which was stressed by Lown and Levine (1955) and recently by Oram and his colleagues (1960) and Harris and his co-workers (1960). In a patient already fibrillating this arrhythmia, like multiple extrasystoles, can only be diagnosed with the electrocardiogram, and more digitalis may be given if it is thought to be uncontrolled fibrillation. It is often difficult to decide whether a patient needs more digitalis or less digitalis but, if a patient who has been on the same dose for a long period develops an arrhythmia or an existing arrhythmia is increased, it is usually wiser to stop the digitalis temporarily and give potassium unless the electrocardiogram, or the proved absence of potassium depletion, makes it clear that more digitalis is needed.

Intractable heart failure.—The aldosterone antagonist, spironolactone, when used with diuretics encourages sodium loss with limited potassium loss from the tubules but in severe cardiac œdema it is often disappointing, probably due to poor glomerular filtration, compared with its effect in ascites due to cirrhosis and in nephrotic œdema. In intractable œdema the mercurials are often more effective than oral diuretics and Domenet and his colleagues (1961) report good results in 28 of 31 such cases with mercaptomerin combined with intravenous aminophylline. When drugs fail it is useless and dangerous to persevere with them without estimation of electrolytes. Rest alone is sometimes followed by a spontaneous diuresis and there is still a place for removal of dependent œdema by mechanical means. When treatment is only effective by frequent adjustments determined by laboratory control it is because of the severity of the heart failure and with this poor prognosis excessive treatment may only cause unnecessary suffering. The treatment of heart failure is more rewarding when it is early.

CONGENITAL HEART DISEASE

Improved recognition of congenital heart disease has shown that this is not a rarity and its incidence is estimated at 5 per 1000 births. The more severe and complicated types may not survive the first few weeks or months but others—particularly the persistent ductus which may be suspected by the wide pulse but does not have the continuous murmur at this age—may be good surgical risks. These infants should be referred to special centres where the means of diagnosis and surgery are available. Innocent murmurs are common in infants and children but many are not innocent and may indicate severe but curable disease. The absence of symptoms is a hazard and to wait until these appear, or until arrested development makes the severity obvious, may mean that the optimum time for surgery is past or that operation is no longer possible. Such a child may later be justified in reproaching parents and doctor for denying him the chance of normal survival. In congenital aortic stenosis particularly, sudden death while at play

is not uncommon and a degree of left ventricular failure which in an adult would produce cardiac asthma and pulmonary œdema can occur in children without complaint. Full assessment, if necessary with cardiac catheterization, can do nothing but good, for it is no less important for the future of a child to know that the defect is mild and will be well tolerated, than it is to confirm that it is severe.

MISCELLANY

There has been an increasing acceptance of the proved effectiveness of penicillin as a prophylactic against rheumatic heart disease in susceptible subjects. Protection against subacute bacterial endocarditis when teeth are extracted is well known but prophylactic care of the teeth against the need for extraction is not so widely practised. Anticoagulants for embolism in rheumatic disease are protective, as is mitral valvotomy in suitable cases. Alcohol is one of the causes of cardiomyopathy (Brigden, 1957), and this has been emphasized by Evans (1959). Repeated subacute pulmonary embolism associated with thrombophlebitis in the legs is now recognized as one of the causes of pulmonary hypertension and may occur in young women following childbirth. Early diagnosis is essential to arrest or cure this serious condition by anticoagulant therapy.

References

Aber, C. P., and Jones, E. Wyn (1960): *Brit. Heart J.*, **22**, 723.
Bjerkelund, C. J. (1957): *Acta med. scand.*, **158**, 330.
Boyd, A. M. (1960): *Angiology*, **11**, 10.
Brigden, W. W. (1957): *Lancet*, **ii**, 1179, 1243.
Crawford, T., Dexter, D., and Teare, R. D. (1961): *Ibid.*, **i**, 181.
Dollery, C. T., Smith, D. Emslie, and Milne, M. D. (1960): *Ibid.*, **ii**, 381.
Domenet, J. S., Evans, D. W., and Brenner, O. (1961): *Brit. med. J.*, **i**, 1130.
Evans, W. (1959): *Brit. Heart J.*, **21**, 456.
Gavey, C. J. (1957): *The Practitioner*, **179**, 398.
Gilchrist, A. R. (1960): *Brit. med. J.*, **i**, 215.
Harris, E. A., Julian, D. G., and Oliver, M. F. (1960): *Ibid.*, **ii**, 1409.
Hayward, G. W. (1961): Personal communication of work shortly to be published.
Kouwenhoven, W. B., Jude, J. R., and Knickerbocker, G. G. (1961): *Mod. Conc. cardiov. Dis.*, **30**, 639.
Leishman, A. W. D., Matthews, H. L., and Smith, A. J. (1959): *Lancet*, **ii**, 1044.
——, ——, —— (1961): *Ibid.*, **ii**, 4.
Lown, B., and Levine, S. A. (1955): 'Current Concepts in Digitalis Therapy', London.
Mackenzie, J. (1911): *Heart*, **2**, 273.
McMichael, J., and Parry, E. H. O. (1960): *Lancet*, **ii**, 991.
Medical Research Council Report (1959): *Brit. med. J.*, **i**, 803.
Morgan, T. N. (1961): *The Practitioner*, **186**, 22.
Müller, O., and Rørvik, K. (1958): *Brit. Heart J.*, **20**, 302.
Oram, S., Resnekov, L., and Davies, P. (1960): *Brit. med. J.*, **ii**, 1402.
Owren, P. A. (1959): *Lancet*, **ii**, 1159.
—— (1961): 'Symposium on Anticoagulant Therapy', London, p. 118.
Prinzmetal, M., and Kennamer, R. (1954): *J. Amer. med. Ass.*, **154**, 1049.
Proceedings of Conference on MER 29 (1960): *Prog. cardiov. Dis.*, **2**, 485.
Sokolow, M., and Perloff, D. (1961): *Circulation*, **23**, 697.
Taylor, S. H., and Donald, K. W. (1960): *Lancet*, **ii**, 389.
Towers, M. K., and Wood, P. (1958): *Brit. med. J.*, **ii**, 1067.
Withering, W. (1785): 'An account of the Foxglove and some of its Medical Uses', Birmingham, p.1, p.11.
Wood, P. (1961): *Brit. med. J.*, **i**, 1779.

ADVANCES IN ENDOCRINOLOGY

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THE proceedings of two international congresses—the Fourth International Goitre Congress and the First International Congress of Endocrinology—provide a useful basis for a review of advances in endocrinology. As a whole congress was devoted to the thyroid greatest attention will be devoted to disturbances of this gland.

THYROTOXICOSIS

The mechanism of the development of this disorder remains obscure and it is still not known whether the condition is primarily a disturbance of the thyroid or pituitary gland. In spite of much effort little advance was made in the investigation of the pathogenesis of the disease until, in 1958, Adams reported that thyroid-stimulating activity could be detected in the blood of a proportion of patients with thyrotoxicosis. This thyroid-stimulating substance found in thyrotoxicosis differs in several respects from the pituitary thyroid-stimulating hormone (TSH) that can be extracted from normal human pituitary glands but its site of origin and significance remain to be determined. At present we cannot identify or treat the primary disturbance and have to use one of the methods of decreasing the capacity of the thyroid to secrete hormone.

Potassium perchlorate has now become definitely established as a drug for the treatment of thyrotoxicosis. It acts by inhibiting the concentration of iodide in the gland. This effect can be overcome by the administration of excess iodide and it is important to ensure that no iodide-containing medicines are prescribed at the same time. In a daily dose of 1000 mg. it is an effective treatment for thyrotoxicosis (Crooks and Wayne, 1960; Crooks, 1961). It is cheaper than carbimazole. Toxic reactions at first appeared rarely, only amounting to slight gastro-intestinal disturbances or skin rashes (Morgans and Trotter, 1954). As so often happens after more widespread usage, however, occasional dangerous complications became apparent. Cases of leucopenia, agranulocytosis and aplastic anæmia have been described (Hobson, 1961; Johnson and Moore, 1961). It is doubtful whether potassium perchlorate is as yet very widely used in this country and the reports of these cases are certainly disturbing. On the other hand, as the extent of use of the drug is not known it is impossible to assess its liability to cause blood dyscrasias even in comparison with other antithyroid agents. A strong case can be made for notification of all deaths due to agranulocytosis and aplastic anæmia so that the dangers of different drugs in this respect can be more accurately ascertained. Clearly if potassium perchlorate is being prescribed it is important to take the same precautions as in the use of the thiouracil series and to ensure that the drug is stopped at the first sign of any possible toxic effect on the marrow.

I^{131} *therapy* of thyrotoxicosis has been employed extensively in many centres for over ten years and it is becoming possible to estimate its advantages and disadvantages in perspective. There is no doubt about its immediate convenience and safety for the patient. Most disquiet now arises over the long-term effects of this form of treatment. Considerable experimentation has not as yet produced a reliable method of predicting accurately the dose necessary to render the patient euthyroid, and techniques employing the minimum of measurement give results as good as those involving detailed preliminary studies. The incidence of post-therapy hypothyroidism is commonly about 10 per cent. a year after treatment and rises continuously with the passage of time. In a group of patients treated ten years ago at Sheffield the incidence is now 25 per cent. On the other hand, in some resistant cases several doses of I^{131} over a period of a year or two may be required before the patient becomes euthyroid (Blomfield *et al.*, 1959). These are serious disadvantages and in this respect the comparison with surgery is unfavourable. Furthermore, after partial thyroidectomy the thyroid remnant eventually comes to resemble a normal gland in both structure and function whereas the irradiated gland is permanently damaged (Eckert *et al.*, 1961).

Although exposure of the thyroid in infancy to ionizing radiation may predispose to the subsequent development of carcinoma no cases of carcinoma following the use of I^{131} in adult life have so far been reported. The available evidence, however, suggests that the latent period after irradiation is probably twenty years and I^{131} therapy has only been widely used for about twelve years. The irradiation dose to the bone marrow is low and the incidence of leukæmia is not apparently increased by this form of treatment (Pochin, 1960). There is still much to be said for continuing the present policy of restricting, except in special circumstances, this form of treatment to those over 40 years of age. In many middle-aged patients with thyroid enlargement and in good general condition apart from the thyrotoxicosis surgery is the treatment of choice as it offers the prospect of a shorter period of attending hospital for review and a much smaller risk of subsequent hypothyroidism. On the other hand, I^{131} therapy is especially indicated in the frailer patient with cardiac complications, in whom the results can be extremely gratifying (Sandler and Wilson, 1959).

HYPOTHYROIDISM

In most cases of spontaneous myxœdema auto-immune antibodies may be detected in the serum. These are of the same nature as those found in lymphadenoid goitre (Hashimoto's disease) and this suggests that the destructive process leading to failure of the thyroid may be the result of an auto-immune mechanism. The initiation of these events, however, is so far obscure, there are many unsolved problems in the pathogenesis of primary myxœdema and no preventive measures are possible.

The treatment of hypothyroidism with thyroid extract was established

at the beginning of the century and the *British Pharmacopœia* preparation of thyroid tablets has remained the popular choice. The method of standardization described in the *British Pharmacopœia*, however, is not entirely satisfactory and doubt has been cast on the activity of some thyroid tablets (Macgregor, 1961). Thyroxine is the principal hormone secreted by the thyroid gland and is a chemically pure substance so that no difficulties of standardization arise. It may be prescribed as thyroxine sodium tablets B.P., 0.1 mg. being roughly equivalent to the 1-grain (60 mg.) thyroid tablet B.P. The increase in cost of treating a myxœdematous patient with thyroxine rather than thyroid is negligible and there is a great advantage in having a preparation of certain potency. Accordingly thyroxine is to be preferred. There is the theoretical disadvantage that up to 10 per cent. of the thyroid secretion may be in the form of triiodothyronine which is not so firmly bound to plasma protein and this exerts a prompter action than thyroxine. Diotroxin, a preparation containing 90 per cent. thyroxine and 10 per cent. liothyronine sodium B.P. Add. (*l*-triiodothyronine sodium), has been introduced but so far no carefully controlled clinical trials comparing it with thyroxine alone have been published. In practice thyroxine sodium tablets constitute a perfectly adequate substitution therapy.

Anæmia is an occasional complication of myxœdema. In a few cases this may be due solely to the hypothyroidism and this responds to treatment with thyroxine alone. Anæmia of this type, however, is relatively uncommon and more often it is due to concomitant iron or cyanocobalamin deficiency. The incidence of pernicious anæmia in patients with primary hypothyroidism is relatively high: 10 per cent. in a recent survey (Tudhope and Wilson, 1960). Achlorhydria has for long been recognized as common in myxœdema, occurring in over 50 per cent. of cases. The serum cyanocobalamin levels are often depressed below the normal range and it is becoming clear that in addition to the fully developed cases of megaloblastic anæmia there is much subclinical cyanocobalamin deficiency associated with myxœdema. The condition is not corrected by treatment with thyroxine and is due to a permanent disturbance of gastric function. The reason why both the thyroid and stomach should so often be damaged together is not known but both are derivatives of the foregut and can concentrate iodide. From the practical point of view it is important not to overlook pernicious anæmia in patients with myxœdema.

THYROID CARCINOMA

Experimental studies have amply demonstrated that thyroid-stimulating hormone is of considerable importance in the pathogenesis and growth of thyroid carcinomas. There is also now some evidence that the growth of differentiated human thyroid carcinomas can be checked by the administration of sufficient thyroid hormone to suppress pituitary thyrotrophin secretion (Thomas and Burns, 1961). Anaplastic carcinomas do not respond to this treatment. Clearly thyroxine is no substitute for surgery, but may

play a considerable part as an ancillary measure. It is most important to ensure that hypothyroidism is not allowed to develop, as any surviving carcinomatous tissue will then be exposed to excessive levels of thyrotrophin. Indeed, after surgery or I^{131} therapy thyroxine should be given as a routine to all patients with follicular or papillary carcinoma in the maximum dose short of producing overt hyperthyroidism, usually 0.3 mg. a day. This suppression of the pituitary secretion of thyrotrophin is an important prophylactic measure against recurrence and may check the rate of growth in inoperable metastases. It is also advisable in conditions which may be regarded as precancerous: for example, nodular goitres or adenomas treated surgically in patients whose thyroids have previously been exposed to ionizing radiations.

ADRENOCORTICAL DISORDERS

Adrenocortical function after corticosteroid therapy.—The administration of cortical steroids such as cortisone, prednisolone and allied drugs in doses sufficient to diminish an inflammatory reaction leads to depression of the ability of the adrenal to secrete hormone in response to a stimulus. The exact mechanism of this adrenal failure has not yet been fully elucidated. In some cases the adrenals of the patient who has been receiving steroids fail to respond to corticotrophin stimulation or show a delayed response only apparent on the second or third day of stimulation. In other cases, even though there has been prolonged treatment with steroids in high dosage, there is a prompt response to corticotrophin. In them there may be depression of pituitary function with secondary adrenal failure. This may be demonstrated by the administration of metopirone. This drug prevents 11 β-hydroxylation in the steroid molecule and thus inhibits the formation of hydrocortisone. The consequent fall in plasma concentration of hydrocortisone leads to increased release of pituitary corticotrophin and stimulation of the adrenal gland. In the presence of metopirone the adrenal can only form deoxycortone in excess which does not suppress the pituitary but is reflected by a rise in urinary steroid excretion, readily detected by the Norymberski method of measuring 17-ketogenic steroids. Metopirone thus forms an excellent method of measuring pituitary reserve with respect to corticotrophin secretion. This may be diminished in some patients after prolonged corticosteroid therapy and the test is clearly valuable in investigating other types of failure of pituitary function.

The importance of appreciating the risk of pituitary or adrenal failure after corticosteroid therapy needs no emphasis. This complication may arise if the patient is only receiving a small dose and this is not increased to cover a surgical operation or acute illness. Gastroenteritis is an especially dangerous illness in patients receiving steroid therapy. The tablets may be vomited or not absorbed and the fluid and electrolyte loss leads to rapid and severe collapse. Difficulty has been encountered more commonly in a patient who has received a course of corticosteroid therapy and has stopped

treatment either just before admission to hospital or some time previously (Winstone and Brooke, 1961). This may not be revealed in the clinical history and adrenal failure may follow surgery. Pituitary-adrenal unresponsiveness may persist for up to two years after completion of a course of steroids. It is clearly most important that information about previous treatment should be readily available in these patients. Many now carry cards providing the necessary information and the Ministry of Health is producing a card for issue to patients who have received steroids. If a severe acute illness develops or a surgical operation is required in these circumstances cortisone should be administered to cover the danger period. It is impossible to make precise statements about the dose required, but 100 to 150 mg. a day should certainly be adequate particularly if it is given before any collapse supervenes. This should be gradually reduced as convalescence proceeds. If the previous treatment was unsuspected and a crisis supervenes hydrocortisone sodium succinate should be given intravenously without delay.

ALDOSTERONE AND ALDOSTERONE ANTAGONISTS

The identification of aldosterone as a naturally secreted adrenal steroid having a powerful action on electrolyte metabolism has led to detailed study of its importance in clinical medicine. Oversecretion of aldosterone may be due to an adrenal adenoma or hyperplasia of the cortex. Primary aldosteronism of this type, first described by Conn, is associated with excessive urinary excretion of potassium, hypokalæmia, sometimes hypernatræmia, muscular weakness and hypertension. Surgical treatment is indicated in these cases. It is now also recognized, however, that an increased secretion of aldosterone may occur as an associated phenomenon in other diseases. This secondary aldosteronism may play a part in determining some of the clinical features and the response to treatment, particularly with diuretics.

At present two possible methods are available for checking increased aldosterone activity. An attempt may be made to block the secretion of aldosterone by administering metopirone. This normally leads to the production of excess deoxycortone which is strongly salt-retaining and thus no therapeutic benefit is derived from giving metopirone alone. If, however, a glucocorticoid such as prednisolone is given along with the metopirone there is no pituitary stimulation and the production of both aldosterone and deoxycortone is inhibited (Holub and Jailer, 1960). This is an interesting approach to the problem but metopirone is liable to produce unpleasant dizziness as a side-effect and in our hands the combined administration of metopirone and prednisolone has not proved as satisfactory as the alternative method of using spironolactone. This agent serves as a competitive antagonist of aldosterone at its site of action on the distal renal tubule.

Spironolactone has been employed extensively to potentiate the action of thiazide diuretics and mersalyl, especially in the treatment of œdema due to hepatic cirrhosis or nephrosis. These clinical conditions may be associated

with considerable secondary aldosteronism so that whenever a diuretic is given there is excessive urinary excretion of potassium rather than sodium (Edmonds, 1960). Spironolactone given alone has little action in these cases and it is essential to give at the same time a diuretic such as chlorothiazide or mersalyl which acts on the proximal tubule so that a large volume of sodium chloride and water is delivered to the distal tubule. In the presence of excess aldosterone much of the sodium is exchanged for potassium but if the action of the aldosterone is prevented by spironolactone the sodium diuresis is preserved. Combined therapy of this type has proved most useful in the treatment of ascites and has greatly reduced the necessity for tapping of the effusion. Spironolactone is administered in tablet form by mouth and a thiazide diuretic should be given at the same time. The usual starting dose of spironolactone is 400 mg. a day but the full effect is usually not seen until after a few days' administration. In a few patients much larger doses, up to 2 g. a day, may be required. Although combined therapy of this type will provoke a sodium rather than potassium loss in the urine, spironolactone administration is an ineffective method of correcting a potassium deficiency and potassium supplements should always be given in treating these patients. Spironolactone itself is remarkably free from toxic effects and many patients have now received treatment for a year or more, but careful supervision is essential in treating patients with ascites as hepatic coma or uræmia is readily precipitated by any electrolyte imbalance resulting from diuretic therapy.

DIABETES MELLITUS

Much recent research has centred on the determination of insulin activity in the blood in healthy people and in diabetic patients. This work has recently been fully reviewed by Vallance-Owen and Wright (1960) and Vallance-Owen (1961). It is clear that an insulin antagonist bound to plasma albumin normally occurs in the blood but that in diabetes mellitus it is present in greater concentration (Vallance-Owen and Lilley, 1961). Its presence prevents the true determination of the total amount of insulin in the blood by bio-assay techniques. Anti-insulin activity in diabetes mellitus is probably of fundamental importance but at present we are largely ignorant of the nature of the antagonist and its mechanism of action. Further investigation of these points may open the way to the preventive treatment of diabetes and its serious complications.

The indications for the use of the sulphonylurea derivatives, such as tolbutamide and chlorpropamide, have now been fairly clearly defined. There is general agreement that they are valueless, and indeed dangerous, in the severe young diabetic liable to ketosis. In this group of patients no insulin activity can be detected in the blood although the presence of insulin antagonists is readily demonstrated. In older aketotic diabetic patients the oral agents are often effective. Insulin activity can be demonstrated in their plasma before treatment and enhanced levels are found after the administration of tolbutamide. The sulphonylureas are inactive in the treatment of

diabetes following total pancreatectomy. The rate of destruction of exogenously administered insulin, at least in man, is not influenced by these drugs. They decrease the rate of release of glucose from the liver but this is probably a secondary effect arising from increased insulin production rather than a direct action on hepatic enzyme systems. The sulphonylureas require the presence of some functioning islets for their action and the balance of evidence from acute experiments favours the view that their effect is largely due to an increased secretion of insulin from the surviving islet tissue.

The prospect of success with oral hypoglycæmic agents is greatest in the mild or moderate older diabetic who cannot be controlled by diet alone. They are no substitute for weight reduction in the obese. In properly selected patients they can afford good control of the glycosuria with corresponding relief from symptoms such as thirst, polyuria and pruritus. So far there is no definite information about their influence on retinal, neural and renal lesions. Good control of the diabetic state is the best preventive measure and provided this can be achieved by oral agents there is no evidence to suggest that they have any influence, deleterious or otherwise, on the development of complications.

Tolbutamide is the drug most widely used. Considering the extent of its employment toxic effects are remarkably rare. Occasionally digestive disturbances or skin rashes may occur. Bone marrow disturbances are uncommon but a few cases of leucopenia, agranulocytosis and thrombocytopenia have been reported. A diet of carbohydrate content in the range 100 to 150 g. is usually prescribed and if glycosuria persists but no ketonuria is present tolbutamide, 1 g. morning and evening, is started. The full effect may not be apparent until treatment has been given for a few days. The dose may then be adjusted to the minimum necessary to ensure control as judged by blood and urine glucose estimations. In a few patients 3 g. a day may be required but this dose should not be exceeded.

Chlorpropamide is probably slightly more liable to give rise to toxic reactions and in particular it may occasionally cause liver damage and jaundice. It has a more persistent action so that only one daily dose is required. The usual starting dose is 250 mg. but again a week or so is required to assess the full effect and the dose may then be adjusted. The minimum necessary should be employed.

In view of its lesser toxicity tolbutamide should probably be regarded as the first choice among the hypoglycæmic agents, but some patients may develop tolerance and become unresponsive to its action. Chlorpropamide may be effective in patients resistant either initially or later to tolbutamide and this wider range of activity makes it a useful drug.

Many other substances are known to possess hypoglycæmic activity but in general they have been found, in the dose necessary to lower the blood sugar, too toxic for use in the treatment of diabetes mellitus. Interest recently has been directed to the biguanides of which the most widely used is phenformin. This substance lowers the blood sugar in most patients with

diabetes and in normal animals but healthy humans are resistant to its action. Gastro-intestinal side-effects are common, particularly if the adult dose exceeds 200 mg. daily. The mechanism of action of phenformin is obscure but there is some evidence that it increases peripheral glucose utilization and decreases hepatic gluconeogenesis. It has an entirely different action from the sulphonylureas and may have some effect in all types of diabetes. It may be combined with insulin therapy and may make control easier with lower doses of insulin, but there is a wide variation in opinion regarding its place in the treatment of diabetes; much more clinical investigation and experience are required under carefully standardized conditions. Duncan and Baird (1960), Marble (1961) and Oakley (1961) have provided recent reviews of oral hypoglycæmic agents.

HUMAN GROWTH HORMONE

One of the most interesting developments in the study of pituitary hormones in recent years has been the demonstration of a definite species specificity in growth hormone. Hormone prepared from human or primate pituitaries is metabolically active in man but bovine hormone is not. Many preparations have been made and their use in the treatment of pituitary dwarfism is being investigated in several centres. Human growth hormone can be assayed in the blood, at least when it is present in excess, and the way is now prepared for considerable advances in this field.

References

Adams, D. D. (1958): *J. clin. Endocrin.*, **18**, 699.
Blomfield, G. W., *et al.* (1959): *Brit. med. J.*, **i**, 63.
Crooks, J. (1961): *The Practitioner*, **186**, 256.
——, and Wayne, E. J. (1960): *Lancet*, **i**, 401.
Duncan, L. J. P., and Baird, J. D. (1960): *Pharmacol. Rev.*, **12**, 91.
Eckert, H., *et al.* (1961): *Clin. Sci.*, **20**, 87.
Edmonds, C. J. (1960): *Lancet*, **i**, 509.
Hobson, Q. J. G. (1961): *Brit. med. J.*, **i**, 1368.
Holub, D. A., and Jailer, J. W. (1960): *Ann. intern. Med.*, **53**, 425.
Johnson, R. S., and Moore, W. G. (1961): *Brit. med. J.*, **i**, 1369.
Macgregor, A. G. (1961): *Lancet*, **i**, 329.
Marble, A. (1961): In 'Annual Review of Medicine', edited by D. A. Rytand, p. 135.
Morgans, M. E., and Trotter, W. R. (1954): *Lancet*, **i**, 749.
Oakley, W. (1961): In 'Modern Trends in Endocrinology' (second series), edited by H. Gardiner-Hill, London, p. 166.
Pochin, E. E. (1960): *Brit. med. J.*, **ii**, 1545.
Sandler, G., and Wilson, G. M. (1959): *Quart. J. Med.*, **28**, 347.
Thomas, C. G., and Burns, S. D. (1961): 'Advances in Thyroid Research' London, p. 361.
Tudhope, G. R., and Wilson, G. M. (1960): *Quart. J. Med.*, **29**, 513.
Vallance-Owen, J. (1961): In 'Modern Trends in Endocrinology' (second series), edited by H. Gardiner-Hill, London, p. 124.
——, and Lilley, M. D. (1961): *Lancet*, **i**, 806.
——, and Wright, P. H. (1960): *Physiol. Rev.*, **40**, 219.
Winstone, N. E., and Brooke, B. N. (1961): *Lancet*, **i**, 973.

ADVANCES IN THE TREATMENT OF DISEASES OF THE BLOOD

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In the past five years there have been disappointingly few advances in treatment to match the remarkable advances in knowledge which have been made in the last ten years or so. Accordingly this article is mainly concerned with a reassessment of established modes of treatment. As more and more potent and specific therapeutic agents become available it becomes increasingly important that accurate diagnoses be made before they are applied. Never before, perhaps, has clinical judgment been of greater importance.

IRON-DEFICIENCY ANÆMIA

Oral ferrous sulphate, conveniently dispensed in pill form, remains the cheapest and most satisfactory preparation for general use. There is no convincing evidence that any of the more expensive organic preparations is more readily absorbed, more fully utilized, or better tolerated. That much of the alleged intolerance to oral iron is psychological has often been demonstrated: for instance, when ferrous sulphate is dispensed as white instead of green tablets the incidence of intolerance has been shown to be much lower. Intolerance, however, is often due to overdosage: there is rarely need to give more than one standard pill twice or thrice a day; this will provide more iron than the bone marrow can utilize for hæmoglobin synthesis in all but those rare patients with a severe defect of iron absorption. To start treatment with two pills thrice a day may well cause intolerance and difficulty is likely to be encountered in such patients whenever iron therapy is subsequently prescribed. On the other hand, there are certain patients who genuinely cannot tolerate oral iron preparations: they may for instance induce symptoms in some patients with active peptic ulceration and after gastric resections or gastroenterostomy: patients with a colostomy may develop a very embarrassing diarrhœa.

A satisfactory fluid preparation is ferrous sulphate mixture B.P.C. If it is given well diluted with water after meals it is very well tolerated. Sometimes ferrous gluconate will be accepted in place of ferrous sulphate but the use of more expensive preparations is rarely justified. The only substance which will certainly promote the absorption of iron is ascorbic acid and this may be given with oral iron pills or dispensed with ferrous sulphate in fluid form: this is likely to be indicated after gastric resection when the absorption of oral iron may be defective. The amount of ascorbic acid given is usually 200 to 500 mg.

There is no justification whatever for expensive compound iron pills containing any other vitamin; normal diets contain more than enough of

such trace elements as copper and manganese. Scale preparations are obsolete.

In the past few years further reports have been published of fatalities in children who have taken large numbers of iron pills in mistake for sweets. All patients given iron pills must be warned to keep them in a safe place.

PARENTERAL IRON

Parenteral iron therapy may have to be considered in rare patients with genuine intolerance to oral iron, in other patients—also rare—who have some form of malabsorption syndrome, and in occasional awkward patients who neglect to take oral preparations. There is also justification for parenteral administration when it is desirable to replace iron stores rapidly as in late pregnancy. Intolerance to oral iron may be encountered both in early and in late pregnancy but this is quite often due to the excessive doses favoured by many obstetricians.

It is often assumed that the response to parenteral iron will be more rapid and complete than to oral preparations. Any slight advantage in favour of parenteral iron, however, is not sufficient in itself to justify its use in place of oral therapy. Preparations of parenteral iron are available for both intramuscular and intravenous administration. The intramuscular route has fallen out of favour in recent years because of the observation that rats and mice may develop a sarcoma at the site of intramuscular iron injections. No analogous human case has been described, but it is not surprising that there have been misgivings. As has been noted, clear indications for parenteral iron therapy are not commonly encountered, and it seems a pity to deny intramuscular iron therapy to patients who would certainly benefit from it because of a very remote and probably negligible risk. The intravenous route has obvious disadvantages and it is unfortunate that reactions—sometimes very severe—are much more common than after intramuscular iron injections. The incidence of these reactions can be greatly reduced by limiting each dose to 100 mg., and by always giving an initial test dose of, say, 25 mg. to ensure that the patient is not unduly sensitive. Because of the severe irritant effect of intravenous iron preparations on the tissues it is essential that there be no leakage at the injection site.

The main advantage of parenteral iron is the speed with which iron storage deposits can be replaced; this can be only slowly achieved by oral iron. In most cases there is no particular urgency, and except when there are very clear indications, oral therapy is always to be preferred in iron-deficiency states.

PERNICIOUS ANÆMIA

In the past few years there has been much interest in the treatment of patients with pernicious anæmia by oral preparations. The original therapy for pernicious anæmia introduced by Minot and Murphy was raw liver in massive oral doses, the efficacy of which depended upon their content of cyanocobalamin. It is possible to maintain patients for long periods, if not permanently, on daily oral doses of the pure vitamin; most patients so treated

will remain in good health with no evidence of clinical or hæmatological relapse and without the development of signs or symptoms of neurological disease. Unfortunately, many patients treated in this way do not attain satisfactory levels of cyanocobalamin in the serum and some are found to have perilously low values. In one recent series it was found that only at a dosage of 1000 mcg. a day could oral treatment achieve full clinical and hæmatological remission and at the same time assure a really satisfactory serum cyanocobalamin level. Such treatment is, of course, expensive and wasteful. If given at lower doses—say, 100 to 200 mcg. a day—periodic cyanocobalamin assays must be made on the serum. The great danger is of the insidious onset of neurological complications in the presence of misleadingly normal hæmatological values.

Since the essential lack in pernicious anæmia patients is of the gastric intrinsic factor it would seem reasonable to give intrinsic factor preparations with or without added cyanocobalamin. Crude oral preparations of hog gastric mucosa are available and are clinically effective; this form of therapy is not, however, very convenient and is not generally favoured. More recently purified preparations of intrinsic factor with cyanocobalamin have been marketed and the initial results seemed very promising. Unfortunately many patients become unresponsive after a while due to the development of antibodies against the foreign intrinsic factor. Certain other complexes of vitamin B_{12} have been tried but there is no clear evidence that they have any particular advantage over cyanocobalamin itself.

It is generally agreed that by far the most satisfactory and safe way of treating patients with pernicious anæmia, or with the neurological complications of cyanocobalamin deficiency, is by parenteral injection of the pure vitamin. The advantages of this are that known amounts of the vitamin are administered and regular therapy is more likely to be ensured, for it is easy for a patient in complete remission to neglect his daily dose of an oral preparation. The monthly visit of a patient to his doctor or district nurse is an additional safeguard; the regular injection is not likely to be missed and the onset of any complications is likely to be noticed early.

MEGALOBLASTIC ANÆMIAS OTHER THAN PERNICIOUS ANÆMIA

Not all patients with a macrocytic hyperchromic anæmia resembling that of pernicious anæmia have a deficiency of cyanocobalamin or of folic acid with megaloblastic change in the bone marrow, and before treatment is started the nature of the anæmia must be established.

The presence of megaloblasts should be sought either in a blood film, buffy coat film, or marrow aspirate; if erythropoiesis is not megaloblastic no response can be expected to follow the administration of cyanocobalamin or folic acid. If megaloblasts are present the nature of the deficiency should then be determined either by direct estimation of the level of cyanocobalamin in the serum or by a clinical trial.

Every now and then cases occur due to malabsorption or following various gastric operations. The diagnosis of these may be easy if there are prominent intestinal symptoms or if there is a history of an abdominal

operation. Some patients with the sprue syndrome, however, have but little diarrhœa and may even be constipated. The correct treatment of these patients—whether it be with cyanocobalamin or folic acid—can only be undertaken after assessment of the nature of the patient's deficiency or deficiencies; some may need iron as well.

Megaloblastic anæmia of pregnancy or of the puerperium is fairly common but the diagnosis may be difficult because the peripheral blood findings may at first resemble those of an iron-deficiency anæmia. Failure to respond to iron should raise a suspicion of the true diagnosis, as should soreness of the mouth and tongue or persistent vomiting and loss of appetite occurring in late pregnancy or in the puerperium. Treatment is by folic acid at a dosage of 5 to 10 mg. daily; maintenance treatment is not needed but occasional patients will develop the condition again in a later pregnancy.

MARROW APLASIA

Many of the chemical agents used for the treatment of malignant disease may cause marrow depression or even severe aplasia if given in excessive or unduly prolonged dosage. Much has been written recently about the transfusion of hæmopoietic cells in an attempt to recolonize the depleted marrow spaces. A convenient source of such cells is fœtal liver; one advantage of these cells is that they do not recognize their environment as foreign and so do not generate antibodies against the host cells. It has been shown that infusions of such cells can become active for a while and may contribute towards the patient's survival. The prognosis of such patients is likely to be very poor but a sufficient number have shown improvement to make the method a promising one. For most cases of aplastic anæmia, whether idiopathic or drug-induced, the only practicable method of treatment is repeated blood transfusion in the hope that the condition may eventually recover. A trial of steroid therapy is often recommended, and sometimes induces a worth-while improvement in the blood values or reduces transfusion needs. Several reviews, however, have repeated warnings about the hazard of infection in patients with aplastic anæmia treated with long-term steroids; such therapy not infrequently contributes towards the death of the patient and steroids should not be continued unless there is some clear indication.

POLYCYTHÆMIA VERA

No new form of therapy has been developed for this condition. By far the most satisfactory treatment for the great majority of patients is radioactive phosphorus. Venesection is often of great value in producing a rapid fall in blood volume when this is desirable before radioactive phosphorus can become effective. Certain of the alkylating agents related to nitrogen mustard have been suggested for the treatment of this condition but they seem to have little to commend them.

MYELOPROLIFERATIVE SYNDROMES

Polycythæmia vera, which is often included under this heading, has already

been mentioned: the term includes a wide range of disorders such as myelofibrosis, a striking feature of which is myeloid metaplasia. Clinically, patients with these conditions may present in many ways and their management requires a nice assessment of many factors such as the precise role of the spleen and in particular the degree of hæmolysis which may be present. New techniques for the investigation of these patients have been developed in recent years but it is not possible to discuss these here; correct treatment can only be applied after careful investigation.

CHRONIC MYELOID LEUKÆMIA

In the opinion of many authorities radiotherapy was the best form of treatment for this condition. In recent years, however, there have been many reports of the efficacy of busulphan. This agent has the great advantages that it can be carefully controlled in graduated doses and that it can be given to outpatients, only occasional visits to hospital being necessary. The drug should be given according to the patient's weight, the usual initial dosage being 0.06 mg. per kg.; this means that a 60 to 70 kg. patient would be given 4 mg.—the dose being given to the nearest 0.5 mg. Although the drug is very convenient for the patient, the physician must have periodic blood counts carried out and the results of therapy must be carefully charted. It must be emphasized that drugs such as busulphan are potentially dangerous and may produce severe depression of the bone marrow if given in excessive or in unduly prolonged doses. Some patients require continuous maintenance therapy but others only need occasional courses of treatment to keep them in perfect health. An advantage of busulphan is that it can be given when there has been only a moderate increase in the white cell count and before the patient is complaining of any untoward symptoms. Unfortunately, whatever mode of treatment is given to patients with chronic myeloid leukæmia the life-expectancy is not greatly increased and the mean survival time is only some three to four years.

CHRONIC LYMPHATIC LEUKÆMIA

No important new chemotherapeutic agent has been introduced in recent years, but a number of centres have reassessed the value of established forms of therapy. It is generally agreed that large masses of lymph nodes are best treated by radiotherapy. For patients with, say, minor degrees of generalized lymphadenopathy and with a substantially elevated lymphocyte count the agents most favoured are chlorambucil and steroids. It is, of course, understood that many patients with benign chronic lymphatic leukæmia do not need any treatment at all; therapy may, in them, reduce an elevated lymphocyte count but not induce any increase in the hæmoglobin level or any clinical improvement. Chlorambucil is given in a dosage of 2 to 12 mg. a day; it is very free of side-effects but, like all similar agents, it can cause marrow aplasia, and careful supervision is essential to its successful and safe use. Steroid therapy is usually recommended when there is some complication such as an overt hæmolytic anæmia or if there is thrombocytopenia thought

to be due to an auto-immune process. It is in such cases that some of the most dramatic effects of steroids are seen, but their use may often reduce transfusion needs in an anæmic patient without obvious hæmolysis. Steroids may also contribute towards the general well-being of the patient and are often a useful adjuvant to chlorambucil. The dangers of steroid therapy have been emphasized in several recent reviews; they are believed to have contributed to a fatal outcome in 10 of a recently reported series of 31 cases and should not be used without a clear understanding of the risks involved.

Patients with chronic lymphatic leukæmia are very liable to infective complications; a common contributory cause of this is hypogammaglobulinæmia and defective antibody production. The administration of gamma globulin to patients with proven hypogammaglobulinæmia and in whom frequent severe infections are a special problem, may be very effective indeed. Injections of as much as 6 g. may be needed at three- to four-weekly intervals.

ACUTE LEUKÆMIA

There have been no outstanding recent advances in therapy; the principal agents remain the steroids and antimetabolites (mercaptopurine and the antifolics such as aminopterin). Because of the frequency of toxic side-effects, the use of antifolics is limited to children. Some publicity has been given to the treatment of acute leukæmia by total body radiation followed by the transfusion of bone-marrow cells. This technique is still in the experimental stage and its use is limited to a few special centres. Because of immunological difficulties it is not yet a practicable form of therapy, but if these can be overcome it may eventually prove possible to treat patients in this way.

HODGKIN'S DISEASE AND RELATED MALIGNANT LYMPHOMAS

The well-established therapeutic agents for these conditions are radiation, nitrogen mustard (mustine), and chlorambucil. Recently a new agent of some promise has been introduced: cyclophosphamide. It is related to nitrogen mustard but acts locally on tumour cells and is without the troublesome local irritant effects which make the administration of intravenous nitrogen mustard so awkward. Particularly pleasing results have been reported in Hodgkin's disease; in one recent report of 17 patients objective improvement was obtained in 11 (65 per cent.), and 15 (88 per cent.) benefited subjectively. Initial treatment is by the intravenous route in doses of 100 to 200 mg. to a total of 2 to 4 g. Oral therapy is then given in a dosage of 100 to 150 mg. until a satisfactory response is obtained. It can be given for six months if necessary. Toxic side-effects are notably rare but periodic white-cell counts are essential, for leucopenia may occur. Alopecia has been reported. It is pleasing to find that this new drug is sometimes effective in patients who have become resistant to all other forms of therapy. Cyclophosphamide also seems to be of value in the treatment of lymphosarcoma and chronic lymphatic leukæmia. It is particularly encouraging to find that it is also of value in myelomatosis: in one report a third of the patients showed objective improvement.

ADVANCES IN GASTROENTEROLOGY

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In a recent book review in the *British Medical Journal*, the rate of progress in gastroenterology was compared to the rate of growth of a coral reef, in contrast to the more rapid advances in the study of cardiac and pulmonary disease in recent years. To a considerable extent, this evaluation is accurate and valuable. Progress has been slow, but also steady, and important advances have been made in gastro-intestinal physiology and in the pathogenesis, diagnosis and therapy of many gastro-intestinal diseases. Much of the outstanding work in gastric physiology, liver disease, malabsorption syndrome and ulcerative colitis has been admirably discussed in recent issues of British journals. It therefore seems appropriate for this review to emphasize other topics which have received relatively more attention from workers in the United States.

MANAGEMENT OF APPARENTLY BENIGN GASTRIC ULCERS

In the United States, roughly 10 per cent. (5 to 20 per cent.) of patients presenting with an apparently benign gastric ulcer will sooner or later be found to have gastric cancer. Over the years, identification of these cancer-bearing patients by the initial bedside and radiological examination has not been sufficiently accurate. Many authorities have therefore recommended immediate surgical management for all gastric ulcers, usually a subtotal gastrectomy. This approach has not been generally adopted, however, because in past decades the rate of operative mortality approached the incidence of cancer in these patients. In recent years, the surgical mortality for elective subtotal gastric resection has declined to 2 to 3 per cent. in many centres. With the risk of surgery less than the average incidence of cancer, many services have continued their policy of early surgical intervention in all patients with gastric ulcer. This attitude has been reinforced by data showing that the 5-year survival of patients with gastric cancer presenting as a gastric ulcer is in the range of 30 to 40 per cent.

In spite of these impressive considerations, a significant proportion of patients in the United States with apparently benign gastric ulcer are not subjected to early surgery, but are operated on only if a carefully observed trial of medical therapy does not result in healing of the ulcer. This approach, based on the rationale that prompt healing is strong evidence against the possibility of malignancy, has resulted in marked improvement in the accuracy of the preoperative diagnosis of malignancy, as indicated by a recent report in which a 'diagnostic error of 1 to 3 per cent.' is cited (Paustian *et al.*, 1960). Patients are selected for the 'trial of therapy' pri-

marily on the basis of radiological demonstration of an apparently benign gastric ulcer, which is not complicated by obstruction or subacute perforation. Estimation of the acidity of the gastric aspirate is essential. If histamine-fast achlorhydria is noted, surgery should be advised without delay. Cytological and gastroscopic studies should be done when possible, as occasionally positive findings will dictate immediate operation, but the absence of such facilities should not preclude the diagnostic trial.

Although details of the medical programme vary, it is generally agreed that bed rest is ideal, and many services consider admission to hospital essential. A balanced six feeding diet with interval alkali is as effective as the traditional hourly milk-alkali regimen, although the latter may occasionally be required for relief of pain (Doll *et al.*, 1956). There is no general agreement as to the use of anticholinergic drugs. Theoretically, their use would appear to be contraindicated because they inhibit gastric emptying and thus may facilitate the antral mechanism for stimulation of gastric secretion. After three to four weeks of therapy, the barium meal examination should be repeated. For the patient to qualify for further conservative therapy, the size of the ulcer crater should be reduced by at least one-half. After a total of six weeks of therapy, there should be complete healing of the ulcer and reversion of the gastric wall to normal pliability on repeat barium-meal examination. Subsequent follow-up examinations are recommended at the third, sixth, ninth and twelfth months after starting therapy and at yearly intervals thereafter.

The recommendation that incompletely successful medical therapy be terminated after six weeks is admittedly arbitrary. This, however, is the period of therapy most commonly recommended by American authors and represents the best compromise of divergent opinions. There is further support for a trial of therapy of this duration in the data on the time required for the healing of the gastric ulcers. In one group of patients, the average healing time was forty days, with healing in the first four weeks occurring at the average weekly rate of 3 to 5 mm. a week (Steigman and Shulman, 1952).

The schedule of therapy as outlined appears to be most appropriate for patients with small or medium ulcers (up to 2.5 cm.). In the management of larger ulcers, rigid adherence to the schedule will result in premature surgery for many benign, ultimately curable ulcers because of their slower healing time. There are very few data on the course of larger benign ulcers under therapy, and it is difficult to be dogmatic about the extent to which medical therapy should be prolonged. It is clear, however, that surgery should not be unduly delayed if the ulcer fails to show progressive improvement. Another problem in the application of the trial of therapy is that there are significant variations amongst ulcers in the several areas of the stomach. The relatively greater incidence of cancer in greater curve and antral ulcers and the benignity of pyloric canal ulcers have long been recognized. Typical data are those of McGlone and Robertson (1953) involving 342 patients with gastric ulcer. The incidence of cancer in the

various areas was as follows: lesser curve, 7.5 per cent.; fundus, 8 per cent.; pre-pyloric area, 17 per cent.; and greater curve, 56 per cent. In addition, there is an increased incidence of complications as the result of ulcer in the distal part of the stomach as compared with ulcer in the proximal stomach (Palmer, 1957). There is also variation in the accuracy of the initial and follow-up radiological examination of ulcer in the various areas, with antral lesions presenting particularly difficult problems.

The term 'gastric ulcer' clearly covers a heterogeneous group of clinical situations and, in a precise sense, is as obsolete as the term 'peptic ulcer'. Even though these differences in the clinical characteristics of ulcers in the various parts of the stomach are well established, many authors continue to present data about 'gastric ulcer' without regard to location. In order to relate the implications of these regional variations to the management of the individual patient, comprehensive data are needed on the accuracy of diagnosis, response to therapy, rate of recurrence and incidence of malignancy for substantial numbers of patients with ulcers in the several subdivisions of the stomach. The physician dealing with a patient with ulceration in the stomach has the definite responsibility to see the patient through to complete healing of the ulcer or its surgical removal. Application of the 'trial of therapy' has minimized the surgery required for benign ulcer without increasing the possibility of overlooking an ulcerated gastric cancer.

EARLY POST-PRANDIAL SYNDROME

There are several well-defined syndromes which occur in patients following partial or complete gastrectomy. One of the most common is the early post-prandial syndrome, which has been defined as 'a series of signs and symptoms experienced within 15 or 20 minutes after the ingestion of food. These are the sensation of epigastric fullness, distension, increased intestinal motility and occasionally diarrhœa. Accompanying these symptoms may be weakness, pallor, sweating, tachycardia, changes in blood pressure and even precordial pain' (Vanamee, 1960). Characteristically, the symptoms are relieved by lying down. The reported incidence of the syndrome after subtotal gastrectomy varies from 1 to 75 per cent. It is generally agreed, however, that some of the symptoms can be identified in a substantial number of post-gastrectomy patients and that the severity of the symptoms progressively decreases in most patients with the passage of time after operation. In its severe and chronic form, the early post-prandial syndrome occurs, on the average, in about 5 per cent. of patients. The incidence of the syndrome is probably higher after Billroth II procedures than following Billroth I anastomosis.

The first major advance in the understanding of the mechanism of the early post-prandial syndrome was the demonstration by Machella (1949) that oral ingestion of a sufficient amount of hypertonic fluid would reproduce the syndrome in partially gastrectomized patients. It was felt that symptoms resulted from jejunal distension associated with the outpouring of plasma

water in an attempt to moderate the hypertonicity. The second major advance was the report of Roberts and his colleagues (1954) that, coincident with the onset of symptoms after a hypertonic load, a significant decrease in plasma volume occurred. The importance of this observation was underlined by the demonstration that the symptoms of the early post-prandial syndrome could be greatly ameliorated by the infusion of plasma expanders after the ingestion of a hypertonic meal. Later reports have shown that a detectable loss of plasma volume occurs also in asymptomatic post-gastrectomy patients. Whilst the average loss for a group of asymptomatic patients is less than that found in symptomatic early post-prandial syndrome patients, there is considerable overlap between the groups. It would appear that a shift of a certain amount of plasma water is necessary for symptoms to appear, but that additional mechanisms are also involved. The search for understanding of these mechanisms has revealed several interesting data.

(1) The incidence of the early post-prandial syndrome is higher in patients operated on because of intractable ulcer pain than for other indications (Landau *et al.*, 1961).

(2) Patients with the early post-prandial syndrome are reported to have a higher incidence of psychiatric illness than asymptomatic patients (Harvey, 1960).

(3) In an attempt to simulate the plasma volume reduction occurring in the syndrome, a number of post-gastrectomy patients have been studied following placement of tourniquets on both legs. Some patients developed a constellation of symptoms resembling the early post-prandial syndrome. The occurrence of these symptoms in the experimental situation correlated fairly well with the incidence of typical early post-prandial symptoms after a hypertonic load (Hobsley and Le Quesne, 1960).

In spite of extensive investigations, the production of the early post-prandial symptoms is not yet completely understood. All patients with the syndrome have a detectable decrease in plasma volume after a hypertonic load, but a comparable decrease in plasma volume can also be found in many asymptomatic post-gastrectomy patients. The fact that with an approximately equal decrease in plasma volume some patients will experience symptoms and others will not suggests that there is a fundamental individual variation in responsiveness to the fluid shifts. The mechanism by which this variation operates is not clear, but its mediation through the autonomic nervous system has long been suspected.

In the management of the early post-prandial syndrome, the regulation of diet and eating habits is fundamental. Patients should eat at least six meals daily and should minimize the intake of concentrated carbohydrates. Fluids should be taken sparingly at mealtimes and should be consumed between meals. Many patients will improve on this regimen, and will perhaps be additionally benefited by anticholinergics and mild sedation. Patients refractory to this programme have been given a variety of medicaments, but none has been shown to be of persisting value.

There is increasing recognition that a number of the refractory patients may be benefited by a second surgical procedure. Jejunal pouch construction, jejunoplasty and interposition procedures are rarely used. Considerable attention, however, is currently being devoted to two other types of procedure. Improvement in a number of patients has been reported after the conversion of a Billroth II anastomosis to a gastroduodenostomy. This improvement is thought by some to be the result of a coincident narrowing of the stoma, since early post-prandial symptoms are not infrequently seen after a primary Billroth I anastomosis. The value of reconstruction of the anastomosis to produce a smaller stoma has been stressed by many authorities. Although the procedure is technically somewhat difficult, and the immediate postoperative management more complicated, reports such as that of Abbott and his colleagues (1960), in which all patients in a group of 18 so operated were benefited, are impressive.

UNDERNUTRITION AFTER GASTRECTOMY

Following subtotal gastrectomy, roughly one-half of the patients fail to regain their normal preoperative weight and a small number (5 per cent. or less) are severely disabled by undernutrition. It seems clear that these patients do not regain their weight primarily because they do not eat enough food (Vanamee, 1960). Many patients find that restriction of their intake protects them from the symptoms of the early and late post-prandial syndromes. Others seem to have a genuine decrease in appetite whilst a few have annoying symptoms resulting from overdistension of the gastric pouch.

In addition to the undernutrition resulting from the more or less voluntary restriction of food intake, there are abnormalities of absorption of protein and fat in some patients after gastric resection. The nitrogen loss is relatively small and readily compensated by a modest increase in protein intake. Steatorrhœa due to impaired absorption of fat is more important, since the degree of impairment is more marked and the caloric value of the fat higher. Rapid intestinal transit and inadequate secretion or mixing of biliary and pancreatic fluids have been implicated as factors in the malabsorption of fat. That a 'blind loop' syndrome may be important in some patients is obvious from reports of marked improvement in steatorrhœa after a course of antibiotics. Improvement in fat absorption with relatively large doses of dilute hydrochloric acid is of theoretical interest, but of little practical value, since it is unpleasant to take, may cause dental complications and may lead to further ulcer complications (Vanamee *et al.*, 1959).

In the management of these underweight patients, the major effort should be directed towards increasing food intake. Since a high carbohydrate intake may actually inhibit fat absorption and may aggravate symptoms of the early post-prandial syndrome, the diet should be low in concentrated carbohydrates. Meals as often as six times a day are usually necessary. In spite of much interest and encouragement by the physician some patients will not respond to dietary manipulation alone. Anabolic steroids may be of benefit.

For patients refractory to diet and drug therapy, a thorough study is indicated. An occasional patient will be found to have steatorrhœa resulting from a 'blind loop' syndrome due to a partially obstructed afferent loop which can be corrected surgically. For patients with marked refractory malnutrition in whom symptoms of the early or late post-prandial syndrome seem to play a significant part in limiting food intake, consideration should be given to a surgical revision of the stoma or to the type of anastomosis.

DIURETICS IN ASCITES DUE TO LIVER DISEASE

Over the years, many patients with ascites due to liver disease have been successfully managed with conservative measures, including abstinence from alcohol, improvement in dietary intake and restriction of salt intake, administration of organic mercurial diuretics and abdominal paracentesis. Although temporary relief is usually achieved in the majority of patients treated relatively soon after the development of ascites, a significant proportion of patients will ultimately become refractory to therapy and will rapidly reaccumulate fluid after each paracentesis. It has become clear that repeated paracenteses will ultimately result in serious depletion of body protein and electrolyte stores. The search for more effective therapy has led to the trial of many types of surgical procedure. Currently the most practical surgical procedure is some sort of portal-systemic anastomosis, but the rates of operative mortality and postoperative mortality are such that one hesitates to recommend the procedure until all other therapeutic modalities have been tried and found wanting.

Since the majority of patients with ascites will continue to be managed medically, there is much interest in the development and dissemination of two new classes of potent diuretic drugs. The benzothiadiazine group, one of which is chlorothiazide, are effective when administered orally and act on the proximal and distal renal tubules to promote the excretion of sodium and potassium, and, to a lesser extent, 'free water'. The spironolactones are also administered by mouth and have a different mechanism of action. These drugs, the so-called 'aldosterone antagonists', inhibit the action of aldosterone on the distal renal tubule and result in the excretion of sodium and chloride and the retention of potassium. The fact that these new drugs can be administered orally represents an advance in convenience. Of much greater clinical significance, however, is the fact that each of the new drugs has a unique mechanism of action, which differs from that of the older diuretic agents. When the newer drugs are administered simultaneously or in combination with one or more of the older agents, the diuretic effect is additive and may in some instances be synergistic.

Whilst the results of clinical trials with the new agents alone or in combination are quite encouraging, it is clear that a routinely applicable regimen for ascites is not yet at hand. Patients with cirrhosis and ascites are quite variable in their spontaneous excretion of salt and water and in their response to diuretic agents. It must also be remembered that any drug

capable of inducing a significant diuresis is also capable of causing significant complications. Because of the variability of response to a diuretic programme and the fair possibility of complications, the management of the individual patient remains, to a considerable extent, a matter of trial and error.

DETAILS OF MANAGEMENT

In general, patients suitable for outpatient management are those with mild to moderate fluid retention who have relatively stable liver function, adequate renal function and no history of recent illness or other cause of electrolyte depletion. These patients should be examined and weighed repeatedly while receiving drug therapy and should be advised to abstain from alcohol. Obviously, patients will vary in their tolerance of restriction of dietary salt intake. Also, there is a variation in the degree of salt restriction required for diuresis. It therefore seems reasonable to recommend a moderate salt restriction (3 g. a day) at the institution of therapy and to press for more rigid restriction if adequate diuresis is not obtained on the more liberal programme.

Either organic mercurials or benzothiadiazines can be administered on an *outpatient basis* with reasonable safety. Organic mercurials are cheaper and probably more potent, but require injection. When given at intervals of three days or more, potassium depletion is almost never a problem. Some patients who respond poorly to mercurials may benefit from chlorothiazide, 500 mg. twice daily, either continuously or intermittently. When administered continuously, depletion of potassium is a significant hazard, with liver coma and cardiac arrhythmias occurring not infrequently. On our service, supplementary potassium (40 to 60 mEq. per day) is given as four to six teaspoonsful of a 25 per cent. solution of potassium chloride, since we feel that the enteric-coated potassium chloride available to us is not adequately absorbed. In the absence of a diuretic response, the drug should not be given for longer than three or four days, since these unresponsive patients may be losing large amounts of potassium. With weekly estimations of the serum potassium, benzothiadiazine therapy can be continued in the presence of continuing diuresis, until the desired result is obtained.

Pending the results of extensive clinical trials now in progress, the routine institution of spironolactone therapy on an outpatient basis is not recommended. The chief hazard in the use of this drug is the 'low-salt syndrome' which may occur in a significant proportion of patients. After stabilization of the patient's regimen in hospital, its use is feasible on an outpatient maintenance basis, provided weekly electrolyte estimations are available.

Admission to hospital is recommended for those patients who, by virtue of large quantities of ascites, nutritional depletion or a poor response to previously administered diuretics, are more likely to develop complications. The basic programme of hospital management is similar to that already outlined for outpatients, except that estimation of serum and urine electrolytes may be required more often. Some patients will readily respond to the

administration of a single diuretic agent, whilst others will require combinations of agents. Recent reports have described various combinations of spironolactone, benzthiazide, organic mercurial, mannitol and adrenal steroid. No combination of two of these drugs has been shown to be clearly superior and no standard regimen has been widely adopted. A reasonable approach to the patient who fails to respond to a single drug is to try benzthiazide and spironolactone in combination. With this combination, hypokalæmia will rarely be a problem and supplementary potassium unnecessary, provided that serial serum potassium estimations are obtained. If there is no response to this regimen in three days, an organic mercurial should be given. This regime, if effective, may be continued, giving the organic mercurial at two- or three-day intervals. Good results have also been reported with the use, in addition to the spironolactone-benzthiazide combination, of adrenal steroids and also mannitol. These latter drugs have been shown to be particularly effective in the low-salt syndrome that develops after prolonged diuretic administration. It is difficult to predict in advance which of the combinations will be most effective for an individual patient, and, for the present, it seems reasonable to try several combinations in rotation.

Details of the relationship of *abdominal paracentesis* to the treatment of ascites with the newer diuretic agents remain to be worked out. There will almost certainly continue to be a place for paracentesis in the massively distended patient with respiratory distress. The hazards of removing large quantities of fluid from such patients are well recognized and may be minimized by limiting the amount of fluid removed to that necessary to allow reasonably comfortable ventilation.

There will probably continue to be occasional patients who do not respond to intensive and prolonged medical therapy. Although the risks of *portal-systemic shunt surgery* for ascites are considerable, the procedure may be justified, particularly if œsophageal varices are demonstrated.

References

Abbott, W. E., Krieger, H., Levey, S., and Bradshaw, J. (1960): *Gastroenterology*, **39**, 12.

Doll, R., Friedlander, P., and Pygott, F. (1956): *Lancet*, **i**, 5.

Harvey, H. D. (1960): *N.Y. St. J. Med.*, **i**, 1773.

Hobsley, M., and Le Quesne, L. P. (1960): *Brit. med. J.*, **i**, 147.

Landau, E., Sullivan, M. E., Dwight, R. W., and Donaldson, R. M. (1961): *New Engl. J. Med.*, **264**, 428.

Machella, T. E. (1949): *Ann. Surg.*, **130**, 145.

McGlone, F. B., and Robertson, D. W. (1953): *Gastroenterology*, **25**, 603.

Palmer, E. D. (1957): *Lancet*, **i**, 1064.

Paustian, F. F., *et al.* (1960): *Gastroenterology*, **38**, 155.

Roberts, K. E., Randall, H. T., and Farr, H. W. (1954): *Surg. Forum*, **4**, 301.

Steigman, F., and Shulman, B. (1952): *Gastroenterology*, **20**, 20.

Vanamee, P. (1960): *J. Amer. med. Ass.*, **172**, 18.

——, Lawrence, W., Levin, S., Peterson, A., and Randall, H. T. (1959): *Ann. Surg.*, **150**, 517.

ADVANCES IN THE TREATMENT OF TUBERCULOSIS

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THE global picture of tuberculosis is still one of a disease of major importance. In western countries, however, the striking decline in death rate, and, to a lesser extent, in incidence, has fostered a hope of its eventual elimination. Whether this is practicable in an age of easy intercommunications while there are countries with a high rate is doubtful.

PREVENTION

In an affluent society the factors of poverty, poor housing and malnutrition are less obtrusive though still there. The direct attack rests on effective treatment of tuberculous patients, more intensive case-finding, BCG vaccination of susceptibles and those at risk and perhaps the future use of prophylactic chemotherapy. Treatment of patients is dealt with subsequently, but it may be said here that the existence of a category of drug-resistant individuals is regarded as one barrier to the elimination of the disease, for, though the mortality is greater in these than in drug susceptible individuals (Thomas, 1961), their recalcitrance to conversion constitutes a danger—exemplified by the presence of resistance to one or more drugs in some newly diagnosed patients.

Case-finding has gone beyond the established procedures of the clinic in an attempt to discover the reluctant or 'hidden' patient. He can be found among special groups, such as immigrants and casuals, or in the community as a whole. Miniature mass radiography is finding its place and, whilst mobile units must be available for emergency surveys, or for use in isolated districts or for mass attack on 'black spots' (as in Glasgow and Liverpool), static units in big towns, sited at a general hospital or clinic, will give a better return. They are used for 'practitioner referrals'—patients with any degree of chest symptoms—for large contact surveys and for applicants from the general public. Emphasis is on elderly males, in view of their high peak in incidence and liability to bronchial carcinoma.

Concentration on the floating population of common lodging-houses and reception centres opens up a source of cases who of their nature are more dangerous than more stable members of the community (Marsh, 1957). From another angle, as the tuberculin-positive rate falls and recedes from childhood and youth, it becomes more feasible to look for the patient who may have caused a primary infection. In the young child this is an obvious measure, and in schoolchildren (now offered a tuberculin test at 13 in State and many private schools) it may be attempted particularly when the reaction

is marked when, as shown by the Medical Research Council BCG and vole vaccine trial (M.R.C., 1956, 1959) there is also a need for further observation of such children in whom there is greater liability to subsequent disease. This trial went far to establish the value of BCG vaccination, now in Britain offered to the tuberculin-negative 13-year-olds, as well as other young contacts and older individuals 'at risk' (a case can be made for testing schoolchildren and vaccinating the negatives at 10 rather than 13). In giving BCG, the intradermal method is still used, often with freeze-dried vaccine, which has the merit of not losing strength with storing.

Among newer methods of case-finding is that of Erin (1960) who in a mining town in Glamorgan collected from individuals who confessed to having sputum 1,982 specimens which on culture revealed *M. tuberculosis* in four cases (three in men over 60).

Prophylactic chemotherapy (isoniazid or isoniazid/PAS) is possibly of wider application in countries with a high incidence. Here, Heaf (1956) advocated it for tuberculin-positive children under 10 (and it might be sensible also to use it for 13-year-olds with high tuberculin positivity), recommending tuberculin testing at ages 2, 5, 9 and 12. This in fact is the treatment of primary infection with the aim of preventing subsequent post-primary disease. An example of a different approach is the work of Dormer and Wood (1960) who in an environment of obvious risk, gave isoniazid (300 mg. daily, single dose) to 600 nurses (tuberculin-positive or -negative) of whom in four years only four developed tuberculosis. Here chemotherapy was intended to cope with exogenous infections.

WHERE TO TREAT PULMONARY TUBERCULOSIS

Domiciliary treatment is now widespread. The most striking testimony to its merits was given perhaps by the results of an Indian trial (Tuberculosis Chemotherapy Centre, 1959, 1961) which were not appreciably worse in the case of patients treated at home, usually in unfavourable circumstances, than in those treated in the sanatorium. The need for rest as part of treatment in all cases has also been questioned. A controlled trial (Tuberculosis Society of Scotland, 1960) allocated 115 patients with pulmonary tuberculosis 'of mild degree' (negative sputum and no cavity over 2 cm. in diameter) randomly to either chemotherapy plus bed rest or chemotherapy at work and found that the results were equally good. On the other hand, such trials exercise a control which ensures that the patient takes himself and his drugs seriously. Elsewhere it has been shown that not all individuals can be trusted. Ireland (1960), for instance, found that after twelve months at home only 25 per cent. of 264 patients were keeping to the prescribed regimen. PAS, the least palatable oral drug, is usually incriminated, and there is an easy urine test for its presence using 'phenistix' reagent strips.

Selection of patients for home or hospital treatment rests on the extent and type of disease, social conditions and the character of the individual. In most circumstances, extensive shadows or a cavity over 2 cm. in diameter

demand at least preliminary hospital care. Sensible individuals with limited disease and good conditions at home may be treated there from the start and as chemotherapy will quickly make the sputum negative interruption of contact with children need not be for long. There is, of course, a view (which I share) that it is more satisfactory in most cases to admit to hospital for at least a few weeks' assessment and initiation of drug therapy before deciding to continue with domiciliary treatment.

STANDARD DRUGS FOR PULMONARY TUBERCULOSIS

The triple aim of arresting disease, removing infectivity and forestalling relapse should be achieved in most cases with adequate chemotherapy for a sufficient period of time. Until recently it was thought that routine application of two standard drugs was sufficient, but the realization that there is a percentage—5.1 per cent. in Britain in one survey (Fox *et al.*, 1957)—of previously untreated patients who have primary resistance to one or more of these drugs has led to the practice of using all three until sensitivities are known. This would apply also when the patient had undergone previously a regime of chemotherapy now regarded as unsatisfactory. Starting doses are: streptomycin 1 g., *para*-aminosalicylic acid (PAS) 15 g., isoniazid 200 or 300 mg. daily; the last two in divided doses. Later, if sensitivity to at least two is present, change to one of the following combinations is satisfactory: streptomycin/PAS (15 g. PAS), isoniazid/PAS (12 g. PAS) or streptomycin/isoniazid. In patients over 40, the risk of vestibular damage from streptomycin, particularly if there is renal inadequacy, increases and it may be given in reduced dosage (1 g. thrice weekly, or 0.5 g. daily) if drug-resistance to one of the other two is present, with possibly a third drug from the non-standard series. The ideal is the selection of a pair of safe, effective drugs which the patient can continue without inconvenience at home. Streptomycin sulphate is commonly used, dihydrostreptomycin (with less tendency to vestibular but more to auditory damage) rarely. The use of a cartridge syringe minimizes the chance of development of streptomycin allergy in the administrator.

Trade preparations of PAS, which aim at greater patient acceptability or reduced gastro-intestinal irritation do not all give adequate blood levels. Citron and Kuper (1959) found that sodium aminosalicylate liquid, cachets, granules and effervescent tablets and calcium aminosalicylate cachets gave similar levels, but enteric-coated sodium PAS tablets low, and calcium benzamidosalicylate very low, levels. The last of these is not now acceptable.

Isoniazid has been used in large doses (6 to 9 mg./kg.), but several trials have suggested that the clinical effect is no better than with standard doses and the side-effects (peripheral neuritis) more frequent, though reduced if pyridoxine is given as well. Acetylation of isoniazid is faster in some individuals than others, but clinical results with standard doses do not suggest that this is important in practice.

Hypersensitivity to these drugs (drug fever, drug rash) can be overcome

by desensitization and this may be carried out more safely and quickly under an 'umbrella' of corticotrophin or prednisolone, of which the doses need not be large.

Here, perhaps, may be mentioned the place of corticosteroids in treatment. In an acutely ill patient with advanced disease, given with effective chemotherapy, they can act as a 'life-saver', expediting the control of the disease. The adrenals may take some time to recover, however, so that an infection or injury occurring within a year or so of treatment with steroids may require their exhibition again to meet current demand on the insufficiently recovered glands.

OTHER DRUGS

These are: viomycin, cycloserine, pyrazinamide, ethionamide, thiacetazone, kanamycin, cyanacetohydrazide, oxytetracycline, the sulphones. Some are recent arrivals, others not. The first five have an accepted place as secondary drugs, of use when resistance or some other factor interferes with the choice of a pair of standard drugs. None has had the careful evaluation that was given to the standard drugs in the Medical Research Council trials. Possibly only pyrazinamide has a potency near to that of streptomycin and isoniazid, the others (though ethionamide is still in a trial stage) perhaps nearer to that of PAS.

Viomycin is given usually in doses of 1 to 2 g. twice weekly and with these the potential toxic effects on liver, kidneys, hæmopoiesis and electrolytes are seldom found.

Cycloserine can provide rather protean side-effects (e.g. psychoses, convulsions, dizziness, drug fever) in an appreciable number of patients on an effective dose of 1 g. daily, perhaps more often in older people. Reduction of dosage to 0.5 g. or 0.75 g. reduces complications and may still give useful clinical results.

Pyrazinamide is best given in a dosage of 30 mg./kg. a day to avoid the complication of hepatitis. With isoniazid (and, perhaps, ethionamide) it provides an effective two-drug regime.

Ethionamide (alpha-ethylthio-iso-nicotinamide), the newest drug, may cause gastro-intestinal irritation, minimized by keeping to a range of 500 to 750 mg. a day. It is likely that the higher dose is necessary to prevent development of resistance to a companion drug, which should probably be streptomycin, isoniazid or pyrazinamide.

Thiacetazone, which was developed in Germany in 1946, and not accepted in this country because of numerous possible toxic effects, seems to be staging something of a come-back. An East African trial (East African Hospitals and Laboratories, 1960) showed that thiacetazone (150 mg. a day) was of similar efficacy to sodium aminosalicylate (10 g. a day) as a companion to isoniazid, and toxic effects were not marked. Its cheapness, like that of isoniazid, makes it attractive in less affluent countries with a high rate of tuberculosis.

Kanamycin, developed in Japan, is thought in that country to have

therapeutic value slightly less than that of streptomycin. It has rather similar side-effects, but including auditory damage and possibly greater nephrotoxicity. It is very expensive in Britain.

OTHER ASPECTS OF CHEMOTHERAPY

Assuming the use of a combination of drugs to which the organism is sensitive, what is still required for cure is adequate duration of treatment. With greater knowledge, the period has lengthened and eighteen months seems now a favourite span. This arises from clinical experience of patients (Ross, 1959) and from laboratory search for *M. tuberculosis* in closed lesions after different periods of chemotherapy. The latter have a special significance in relation to possible relapse. Inert, non-culturable bacilli are often found in caseous foci in resected specimens from 'quiescent' cases, but the presence of culturable bacilli does seem to depend on the brevity of the course of drugs previously administered (perhaps excepting those resistant to such drugs). In practice it should be assumed that a year's chemotherapy is the least period of time (for minimal lung disease or tuberculous pleurisy) and that many patients should continue much longer.

These statements refer to patients who have achieved clinical quiescence. What of the patient with a frequent or occasional positive sputum? These will prove to be resistant to at least two of the standard drugs and a problem may arise as to how far one should continue chemotherapy in various permutations in the hope of obtaining eventual negativity. It should be remembered at some stage that there is another person besides the patient who may come forward for consideration in the future—the individual whom he may infect. If all the effective drugs are used in combinations of progressively diminishing power to prevent drug resistance, any future secondary case may have disease which is not susceptible to chemotherapy. This may have to be considered, especially when the patient is an uncertain drug taker. Thomas (1960) found a greater number of resistant cases (to PAS plus isoniazid, or PAS daily plus streptomycin thrice weekly) among those given drugs at home.

In the individual patient, the importance of drug resistance is in its association with poor clinical results. Resistance tests entail a comparison with the effect of a drug on the standard organism, H 37 RV, and many British authorities would change a regime when merely partial resistance appears. In practice, sensitivities are done on diagnosis and again after an interval if chemotherapy has not rendered the sputum negative. Change of regime may be necessary as a result or, indeed, if, despite a negative sputum, clinical progress is unsatisfactory. There are some advocates (outside Britain) for the use of isoniazid alone in certain circumstances, since in the laboratory, isoniazid-resistant, catalase-negative *M. tuberculosis* carry reduced pathogenicity for guinea-pigs which, they say, could apply to human beings also. Another reason for routine drug sensitivities is the rare possibility that what appears to be tuberculous lung disease may in fact be due

to infections with atypical mycobacteria, which are usually resistant, at least partially, to the standard drugs.

SURGERY AND PULMONARY TUBERCULOSIS

The broad stream which flowed in the twenties and thirties has shrunk still further to a narrow brook. Resection of diseased lung is the only definitive operation, though reparative procedures such as decortication for grossly thickened pleura, pleurectomy for empyema and thoracoplasty for closure of intractable post-resection spaces all have a place. Tuberculous empyema is almost a thing of the past. Adequate chemotherapy for a sufficient period will in most cases of lung disease bring about a probable cure even in cavitated lesions, so that ideally surgery would seldom need consideration. When relapse and surgery were debated at the Conference of the International Union against Tuberculosis in 1959, it was apparent that the indications were wider in some centres than in others. All agreed that chemotherapy should be given a fair trial (six to eight months). Accepting that, surgery may be indicated in:—

(1) Localized lesions with persistent positive sputum, especially when resistance to two or more standard drugs is present.
(2) Cavitation which has persisted without hair-line thinning of the cavity wall even with a negative sputum.
(3) Localized bronchiectasis causing symptoms (e.g. recurrent hæmoptysis).
(4) Localized lesions which have relapsed despite previous adequate chemotherapy.
(5) When the patient is likely to return to an unsuitable employment or environment or when he is temperamentally unsuited to persisting with chemotherapy away from hospital control.

Estimations of lung function play an increasing part in the final decision with regard to surgery. Usually, these will be the simpler ventilatory tests, particularly the M.B.C. (maximum volume of air expired per minute), the F.E.V.1 (volume of air expired in one second of forced expiration) and bronchospirometry (providing an estimation of ventilatory function of the separate lungs and their respective capacities to absorb oxygen). An idea can be obtained as to how much lung can safely be surrendered. Little (1956) showed that such loss in an uncomplicated case would average 14 per cent. for segmental resection, 16.3 per cent. for lobectomy, 21.1 to 35.1 per cent. (according to number of ribs removed) for thoracoplasty.

REHABILITATION

The great majority of patients may be allowed to return to their previous skills. Where conditions of employment are unsuitable, the latter may have to be changed and help may be sought from the area D.R.O. (Disablement Resettlement Officer of the Ministry of Labour). A minority will require reorientation and possibly re-training and for these Industrial Rehabilitation Units and Re-Training Centres have a useful place. Prolonged sheltered employment is rarely necessary, but for persistently sputum-positive (often drug-resistant) patients—fortunately few in number—the problem remains difficult.

NON-PULMONARY TUBERCULOSIS

In *tuberculous meningitis*, there are still two opposing camps: those who always include intrathecal streptomycin in the initial treatment, and those who never give it by that route. The latter point not only to the obvious drawbacks of intrathecal streptomycin but to the high diffusibility of isoniazid into the cerebrospinal fluid. Favourable reports come from both groups, but the condition is one which demands very careful grading of cases for comparison. Possibly, as Pines (1960) says, when consciousness at the start of treatment is only slightly or moderately impaired, intrathecal streptomycin is unnecessary. Retrospectively he compared 26 patients at that stage who had received it with 13 who had not and found that the results were equally favourable (though evidently the latter group required a longer duration of chemotherapy). In advanced cases, in which diffusion into the cerebrospinal fluid may be impaired, there is still a strong case for intrathecal streptomycin, and in these, corticosteroids may also be of value. Isoniazid is given in a dose of 10 mg./kg., with PAS 300 mg./kg., and often intramuscular streptomycin during the first weeks.

It is realized now that in *urogenital tuberculosis* adequate chemotherapy for a sufficient time will often produce healing, although, of course, scarring and contraction or stenosis may give rise to complications. Kidney function must be kept in mind if streptomycin is to be used, in case blood levels become dangerously high.

In recent years, *tuberculous endometritis* has received a certain amount of attention, partly because it is responsible for about 8 per cent. of cases of sterility. The cure with drugs unfortunately does not mean a change in the latter condition.

In the early phase of this 'antibiotic era' it used sometimes to be said that drug resistance was less likely to develop in non-pulmonary than in pulmonary tuberculosis, but no-one now would digress from the general principles of chemotherapy whatever the form of the disease.

References

Citron, K. M., and Kuper, S. W. A. (1959): *Tubercle*, **40**, 443.
Dormer, B. A., and Wood, M. M. (1960): *Lancet*, **ii**, 837.
East African Hospitals and Laboratories (1960): *Tubercle*, **41**, 399.
Erin, L. (1960): *Ibid.*, **41**, 363.
Fox, W., *et al.* (1957): *Ibid.*, **38**, 71.
Heaf, F. (1956): *Brit. med. J.*, **ii**, 1383.
Ireland, H. D. (1960): *Amer. Rev. resp. Dis.*, **82**, 370.
Little, G. M. (1956): *Tubercle*, **37**, 172.
Marsh, K. (1957): *Lancet*, **i**, 1136.
Medical Research Council (1956): *Brit. med. J.*, **i**, 413.
—— (1959): *Ibid.*, **ii**, 379.
Pines, A. (1960): *Tubercle*, **41**, 117.
Ross, J. D. (1959): *Bull. int. Un. Tuberc.*, **29**, 710.
Thomas, H. E. (1960): *Tubercle*, **41**, 37.
—— (1961): *Ibid.*, **42**, 1.
Tuberculosis Chemotherapy Centre, India (1959): *Bull. Wld Hlth Org.*, **21**, 51.
—— (1961): *Ibid.*, **24**, 149.
Tuberculosis Society of Scotland (1960): *Tubercle*, **41**, 161.

ADVANCES IN PSYCHOLOGICAL MEDICINE

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A GREAT deal has happened in psychiatry during the past ten years. Psychiatric treatment has undergone quite radical changes, which have been reflected in national statistics of mental disorders. Since the mental hospitals became incorporated in the National Health Service, annual admissions to mental hospitals in England and Wales have risen year by year—from 60,900 in 1949 to over 95,300 in 1959. During the same period, many more patients than before have been discharged after a relatively short stay: for example, more than half of all patients admitted during 1959 were discharged within three months, and three-quarters of them within six months. As a result, the total number of patients resident in mental hospitals has actually been declining from the peak figure of over 152,000 in 1954 to approximately 144,000 in 1959.

MAJOR TRENDS

Major changes in the trends of mental hospital statistics were already apparent in the figures for the first two years of the National Health Service (Registrar General, 1953) and were confirmed in a survey carried out in a limited number of Metropolitan mental hospitals five years later (Carstairs *et al.*, 1955). Subsequent analyses have shown that the new pattern of relatively short inpatient spells, with an increased tendency toward subsequent readmission, is being experienced by schizophrenic and by elderly patients as well as by those who have traditionally been regarded as having a better prognosis (Wing *et al.*, 1959; Morrissey and Sainsbury, 1959). Some observers (particularly in the United States) have attributed the increased turnover of psychiatric patients to the widespread use of tranquillizers; but it is worth pointing out that the mental hospitals of Paris have not shown corresponding changes in spite of the fact that chlorpromazine and several of its successors are the products of French clinical research. The distinguishing feature of British post-war mental hospital practice has been the dramatic liberalization of the conditions under which patients are treated. The open-door policy and the concept of the therapeutic community have both been achieved in many British hospitals with a success which has excited the emulation of our colleagues in North America (Millbank Memorial Fund, 1958). It can fairly be said that British mental hospitals have been among the first to achieve the high standards set in the Third Report of the WHO Expert Committee on Mental Health (1953).

Meanwhile psychiatric outpatient care has also been expanding. Since the 'Appointed Day,' many new psychiatric clinics have been developed in general hospitals: as a result, the number of new outpatients seen by psychiatrists in England and Wales increased from 93,800 in 1949 to 144,300 in 1959: an increase of 54 per cent. During these ten years there was also a remarkable expansion in child guidance work: between 1949 and 1959 there was a more than fourfold increase in the number of children seen at these clinics.

It would be flattering to the self-esteem of psychiatry if we could believe that these major changes in our practice could be attributed (like the equally sweeping changes which have come about in the treatment of tuberculosis, venereal disease and many other infections) to major advances in our understanding and control of illness, but this is only partly true. Few would claim that our current 'wonder drugs' exercise more than a palliative influence on psychiatric disorders. The big change has rather been one of public opinion.

The two most important publications in psychiatry of the last decade have not been research reports or reformulations of etiological theory. They have been the publication of the Report of the Royal Commission on the Law Relating to Mental Illness and Mental Disorder (1957) and the volume entitled 'Action for Mental Health' (Joint Commission on Mental Illness and Health, 1961). The former has already led to a major revision of the law in Britain, and the latter may prove no less influential in shaping future American psychiatric policy. Since the end of the 1939-45 War considerable strides have been taken towards humanizing the conditions under which mental hospital patients are treated, and towards bridging the gap which has long separated psychiatry from the rest of medical practice. It is a matter for pride that Britain has led the world in these matters. In the majority of cases, psychiatric patients can now be treated without legal formalities; and they can be treated in any one of several agencies of the Health Service. This change will probably do more than could ever be accomplished by exhortation, to break down the stigma attaching to mental illness. As is the way in our country, for some years before the new Mental Health Act was passed ingenious means were found to evade the restrictions of the outmoded Lunacy Acts. The pioneer mental health services of Nottingham (Macmillan, 1956, 1960), Worthing (Carse, 1959) and York (Bowen and Crane, 1958) have already provided alternative patterns for the services of the future which will, it is hoped, make possible more efficient coordination of the parts played by the psychiatrist, the general practitioner and the local authority in the treatment of the mentally ill.

In this period of administrative experiment and change, attention should be drawn to Professor McKeown's radical new concept of a 'balanced hospital community' which would cater for *all* the medical needs—for acute, chronic and psychiatric illness—of the population which it serves. This proposal, at first recommended on theoretical grounds (McKeown, 1958) is

now finding practical expression in the new teaching hospital which is being planned in Birmingham (McKeown, 1961).

EPIDEMIOLOGY OF MENTAL DISORDERS

One consequence of the new trend in psychiatric practice has been a revival of interest in the epidemiology of mental disorders. Statistics of the hospitalized mentally ill have been published for more than a century: at first by the Commissioners in Lunacy, then by the Board of Control, and, since 1949, by the Registrar General. In recent years, however, these national statistics have been supplemented by numerous more intensive local inquiries into the prevalence of particular disorders, and into the effect of social factors on their incidence and their outcome. Early studies in this field were carried out by the Medical Research Council's Social Psychiatry and Social Medicine Research Units (to which have recently been added new units concerned with psychiatric genetics, psychiatric epidemiology and with evaluative studies in clinical psychiatry) but they are no longer working alone. When the Nuffield Provincial Hospitals Trust convened a conference in November 1960 on psychiatric epidemiology (MacLachlan, 1961) it was reported that at least 42 research projects in this area were currently under way in Britain (Rawnsley, 1960).

Particular attention has attached to a number of attempts which have been made to predict future requirements of mental hospital beds, taking the trends shown during recent years as a guide (Norton, 1961; Tooth and Brooke, 1961; Cross and Yates, 1961). Most observers are agreed that there will continue to be an increasing deployment of psychiatric effort in outpatient, day hospital, domiciliary and general hospital work and a corresponding decline in the need for mental hospital beds, but many psychiatrists believe that the Minister of Health has been unduly optimistic in predicting that in fifteen years' time we shall require only 50 per cent. of our present complement of these beds.

There is no dispute, however, about the fact that general practitioners are becoming involved to a much greater extent than before in the care and management of the mentally ill. In a recent follow-up study of a group of schizophrenics, Parkes (1961) has found that the majority of these patients were discharged from hospital while still on a maintenance dose of a phenothiazine drug. During the first weeks after their discharge their supervision was shared by the hospitals' outpatient clinics and the general practitioners, but in many cases their attendances soon ceased. In later months, however, when relapses began to occur, it was almost invariably the general practitioner who had to deal with the situation.

After-care is far from being the only aspect of psychiatric treatment in which general practitioners are engaged. During recent years an ever-increasing number of neuroleptic drugs and 'psychic energizers' have been appearing on the market, and the claims of each new product are pressed with all the persuasive power of the advertising industry. It is already

possible to tide over with drug treatment many cases of depression which would formerly have required hospital admission but, as will be shown later, the indications for choosing any particular one of the several anti-depressant drugs have not yet been firmly established.

MINOR PSYCHIATRIC DISORDERS IN GENERAL PRACTICE

Recent years have seen a growing awareness of the large volume of minor psychiatric disorders in the day-to-day work of the general practitioner: estimates vary widely according to the latitude of the definition of psychiatric disorder which is accepted. A working party of the College of General Practitioners (1958) reported a general consensus of opinion that psychiatric disorders account for about 30 per cent. of the practitioner's case-load. More conservative estimates have emerged from *ad hoc* inquiries and using explicit criteria for the identification of cases; thus, Pasamanick and his co-workers (1957) in Baltimore found a point prevalence of 9.3 per cent. for all forms of psychiatric disability on screening a random sample of an urban population. A major defect of this survey was the high non-response rate of 37 per cent.; with psychiatric disorders one can expect particularly high rates among those who show reluctance to cooperate. In Britain the survey of morbidity in 106 general practices by Logan and Cushion (1958) showed that approximately 7 per cent. of patients at risk consulted their practitioner on account of a psychiatric complaint during the year under review. A more intensive survey of the work of one group practice in South London showed a one-year prevalence rate for 'conspicuous psychiatric morbidity' of 9 per cent. of the registered adult population (Kessel, 1960). Psychoneurotic disorders, even narrowly defined, come next to colds, coughs and rheumatism in frequency of appearance in the doctor's surgery; in addition, emotional factors complicate many complaints which present as physical illness.

With the increased recognition of minor psychiatric disorders, many general practitioners have felt the need of brushing up their—often rather rudimentary—student teaching in this area. Some help can be obtained from refresher courses, from the perusal of books (one of the best is still Maurice Levine's 'Psychotherapy in Medical Practice' published twenty years ago (1942), but it now has to contend with Michael Balint's 'The Doctor, his Patient and the Illness (1957)), or from *The Lancet's* recent series of articles on 'Teaching of Everyday Psychiatry,' but it remains unfortunately true that to acquire skill in the recognition and treatment of emotional disorder requires a fairly prolonged apprenticeship with an experienced supervisor. This tiresome necessity is due to the fact that in psychotherapy the doctor's personality is itself an agent in treatment, but an agent whose proper use has to be learned.

Many doctors find the transactions of psychotherapy uncongenial, and wish there were more direct, impersonal methods of treating psychoneuroses. For them, one can recommend the trenchant writings of Eysenck (1959,

1960), who has achieved the remarkable feat of evolving a therapy, based on learning theory and conditioning, while refraining personally from therapeutic contact with patients. It is unfortunate that Eysenck's advocacy of his own psychological theories has been so virulently polemical; his provocative utterances tend to excite partisan reactions rather than the cool spirit of scientific inquiry which he constantly invokes. Characteristically, his recent handbook 'Behaviour Therapy and the Neuroses' consists almost entirely of articles written by his students: there is no contribution by any of the physicians in the Institute of Psychiatry in which Professor Eysenck holds his chair. To many psychiatrists Eysenck's impersonal approach to the patient is frankly repugnant; but this should not be allowed to prevent our putting his theories to the test in systematic clinical trials—particularly in conditions such as phobic and obsessional states, and sexual perversions, where existing methods of treatment are slow and uncertain in their efficacy.

PSYCHOPHARMACOLOGY

The introduction, some seven years ago, of chlorpromazine and Rauwolfia derivatives into the psychiatrist's pharmacopœia has been followed by a deluge of tranquillizing drugs whose biological effects have been succinctly summarized by Vogt (1958). She points out that reserpine-like substances give rise to a reduction in brain tissue of 5-hydroxytryptamine and the catecholamines, substances normally found in high concentration in the hypothalamus, the tegmentum of the midbrain and in parts of the limbic system. Chlorpromazine is an inhibitor of many enzymatic processes—an action which underlies its depressing effect on cortical activity and also its undesirable side-effects on the bone marrow, on autonomic functions and in the development of Parkinsonism. Rauwolfia preparations have fallen into disfavour since they were found to give rise in a few cases to quite severe depressive reactions; attention has been concentrated upon analogues of chlorpromazine in the hope of finding alternative drugs which would have fewer side-effects.

If little is known about the physiological processes underlying the action of reserpine and chlorpromazine, still less can be said with certainty about the mechanism of the series of less toxic drugs for the relief of neurotic symptoms for which their manufacturers claim results verging on the miraculous: drugs such as benactyzine, hydroxyzine and meprobamate, to which has recently been added, with a fresh blaze of trumpets, chlordiazepoxide. At first, it must be confessed, clinicians were over-ready to endorse the makers' sanguine claims for these new drugs. The pitfalls which surround the just evaluation of any new remedy, and the means of circumventing them, have been admirably described in Witts' (1959) 'Medical Surveys and Clinical Trials,' but this teaching was unfamiliar to most psychiatrists. In a witty and perspicacious article, Foulds (1958) surveyed a number of British and American psychiatric journals and pointed out that optimistic claims occurred most often in therapeutic trials which were ill-designed and

lacking in controls. Two years later the authors of a careful study of an anti-depressant drug (Kiloh *et al.*, 1960) found that in a review of over 1000 clinical reports on this drug they could trace only four strictly controlled studies.

There has, however, been a gradual increase in the proportion of clinical reports based on scientifically valid observations. Many of these have produced negative findings, indicating that, as so often in the history of therapeutics, the newest drugs have had an initial success, which could be attributed to suggestibility (acting on both the doctor and his patients), followed by an apparent loss of effectiveness. The degree to which suggestibility can induce physiological change is illustrated by the 'placebo response' which is now so well recognized that it has earned a special review in the *Pharmacological Review* (Wolf, 1959).

Uncertainty in the interpretation of results is greatest in conditions which have a tendency towards spontaneous remission. It has long been known that depressive psychosis has this characteristic. Electric shock treatment (E.C.T.) has been employed for the last twenty years to accelerate recovery from the attack of depression, but it does not give protection against relapse. Much less is known about the natural history of psychoneurosis, but one recent study (Wallace and Whyte, 1959) attempted to ascertain the outcome in 83 psychoneurotic patients who had been promised psychotherapy but who failed to receive it. This follow-up was regrettably incomplete: valid information was obtained on only 49 patients, of whom 65 per cent. showed spontaneous remission of symptoms within three years.

It is precisely in the 'twilight zone' of depressive reactions and neurotic depressions that the new wave of drugs, collectively known as psychic energizers, claim to be therapeutically active; and not surprisingly controlled trials of these drugs have often reported contradictory findings. Two facts can be said to have emerged from our first few years' experience with the monoamine oxidase inhibiting drugs (the first of which to be reported was iproniazid to which have since been added phenelzine, nialamide and pheniprazine) and imipramine. (1) None of these drugs produces immediate remission in acute endogenous depression as consistently as does E.C.T. (2) Prolonged administration, which should be accompanied by tests of liver function, has been shown to lessen the frequency of relapse which attends short-term treatment by either E.C.T. or drugs.

The current state of pharmacological treatment in psychiatry has been wryly epitomized by Jacobsen (1960) in the following terms:—

'We try to treat diseases of which we know next to nothing with drugs of which we know next to nothing.'

In these circumstances the rational thing to do is to suspend judgment, while watching the literature in the hope that a greater consensus of opinion will emerge on the indications for, and the mode of action of, the psychotropic drugs. In the meantime, however, clinicians are constantly finding it necessary to act, basing their decisions upon the best available information

Approved name	Proprietary name	Daily dose (mg.)	Indications	Complications and side-effects
		(a) *Phenothiazine derivatives*		
Chlorpromazine	Largactil	100–1000	For relief of manic or schizophrenic excitement, and for control of symptoms in acute and chronic schizophrenia	Parkinsonism with high doses; hypotension; drowsiness; skin rashes; infrequently jaundice or agranulocytosis
Promazine	Sparine	100–1000		
Thioridazine	Melleril	100–1000		
Acepromazine	Notensil			
Prochlorperazine	Stemetil	30–300		
Trifluoperazine	Stelazine	10–45		
Fluopromazine	Vespral	30–300		
Perphenazine	Fentazin	16–48		
Thiopropazate	Dartalan	15–30		
		(b) *Derivatives of glycerol and other propanols*		
Meprobamate	Equanil, Mepavlon, Miltown	1200–2400	To allay anxiety and tension; insomnia	Drowsiness—a relatively non-toxic group
Mephenesin	Myanesin	1–4 g.		
		(c) *Derivatives of benzhydrol*		
Benactyzine	Nutinal	3–9	Anxiety, and tension states. Psychosomatic disorders involving symptoms such as palpitation, perspiration, premenstrual tension	Should not be used in psychotic states
Hydroxyzine	Atarax	30–60		
Azacyclonol	Frenquel	60–200	Relief of hallucinations in acute schizophrenics and toxic hallucinosis	
		(d) *Derivative of iminodibenzyl*		
Imipramine	Tofranil	75–225	As an alternative to E.C.T. in depression: maintenance doses claimed to reduce relapse rate after recovery from depressive illness. Of debatable value in neurotic depression	Dryness of mouth, trembling, sweating, dizziness, dermatitis
		(e) *Monoamine oxidase inhibitors*		
Iproniazid	Marsilid	150–300	Moderate or severe depression	Toxic jaundice (infrequent) reported with iproniazid and phenelzine. Postural hypotension, sometimes constipation, delayed micturition, loss of libido
Pheniprazine	Cavodil	9–24		
Phenelzine	Nardil	20–60		
Isocarboxazid	Marplan	20–40		
Chlordiazepoxide	Librium	30–60	Agitation, acute anxiety, tension states and obsessional symptoms	Drowsiness, ataxia

TABLE I.—The common neuroleptic and antidepressant drugs.

however imperfect this may be. Table I, summarizing particulars of the commoner neuroleptic and antidepressant drugs, may serve as a guide to current psychiatric practice.

BASIC RESEARCH

The advent of the tranquillizing drugs has given fresh impetus to research on the neuro-physiological substrates of mental illness. In this area, however, as in the reports on drug therapy, there have been many false alarms and unfulfilled promises. Research has been particularly active in relation to schizophrenia. In turn, adrenochrome or a similar breakdown product of adrenaline (Osmond and Smythies, 1952), disorders of amino-acid metabolism (McGeer *et al.*, 1957), ceruloplasmin (Leach *et al.*, 1956) and 'taraxein,' a toxic constituent believed to be present in schizophrenic serum (Heath *et al.*, 1958) have been invoked as elements crucial to the schizophrenic process: but each hypothesis in turn has failed to secure confirmatory evidence (Kety, 1959). An excellent summary of this work has been provided by Smythies (1960).

In contrast, the studies of 5-hydroxytryptamine (serotonin) initiated by Gaddum and his co-workers in Edinburgh (Amin, Crawford and Gaddum, 1954) has led to a fruitful and continuing series of investigations of localized changes in brain biochemistry associated with depression, schizophrenia and psychotropic drug action. A similar restriction of aim is apparent in the work of Frohmann and his group in Detroit, who have taken heed of Kety's methodological strictures in pursuing their studies of disorders of glucose (particularly adenosine-triphosphate) metabolism in schizophrenic subjects. (Frohmann *et al.*, 1960.)

MENTAL DEFICIENCY

It can fairly be said that psychiatry is still looking expectantly towards biochemical research for elucidation of its major biological unknowns. Surprisingly, however, the two major advances in biological understanding have not concerned the functional psychoses, but mental deficiency. It is only in the last few years that phenylketonuria has been shown to be modifiable by the administration of a diet restricted in phenylalanine content (Armstrong and Tyler, 1955; Horner and Streamer, 1956). Still more recently advances in laboratory technique have enabled geneticists to reveal that the normal human complement of chromosomes is 46 and not, as had long been believed, 48; and further studies in this field gave rise to the discovery, almost simultaneously in Paris (Lejeune *et al.*, 1959) and in Edinburgh (Jacobs *et al.*, 1959) that mongols characteristically exhibit an extra chromosome, having a diploid number of 47. These findings have started a regular hue and cry in pursuit of associated genetic anomalies, such as those giving rise to various forms of intersex, and those linked with a predisposition to leukæmia.

Mental deficiency has tended on the whole to be a relatively neglected

field of psychiatric research. It was perhaps for this very reason that Sir Aubrey Lewis chose it as the topic for his Adolf Meyer Lecture to the American Psychiatric Association (Lewis, 1960). His review of research in this area made only passing reference to the latest developments just mentioned, but dealt at length with recent investigations, by Hermelin and O'Connor in London, and by Luria and his associates in Moscow, into the learning processes of mentally handicapped children. As in the case of the genetic studies, this research has general implications which apply to normal subjects as much as to the patients themselves.

The changing current of public opinion to which reference has already been made has influenced the policies governing the care of the mentally defective no less radically than it has the practice of mental hospital psychiatry. Here the social psychiatric research of Sir Aubrey Lewis' own group has contributed valuable information (O'Connor and Tizard, 1957; Tizard and Grad, 1961). In the United States, considerable attention has been drawn to the epidemiological studies of Pasamanick (1959) and Knobloch (Knobloch and Pasamanick, 1959), who claim to have demonstrated that particular disturbances of pregnancy (among which they specifically designate a lowered protein intake on the part of the mother) are associated with high rates for a series of congenital disorders in children, including mental retardation. Their work has not been uncontested but it has the merits of being scrupulously described and reported in full statistical detail, and of giving rise to testable hypotheses. They point the way towards interventions which could, they believe, lower the incidence of these conditions.

Many people have assumed that the prevalence of severe mental defectives in our population must be increasing because modern drugs prolong the life of many severely subnormal children who would formerly have died young. In a recent survey, however, Tizard (1961) has found that, whereas nearly four times as many mongol children now survive to the age of 10, there appears to have been a decrease by nearly one-third in the total prevalence of severe subnormality, as compared with the figures of E. O. Lewis' national survey in 1929. It seems that the improvement in social, health and nutritional standards which has led to striking reductions in the infant mortality rate during the past twenty years has led to a significant diminution in the frequency of births of the severely subnormal—a finding which supports, at least by implication, the contentions of Pasamanick and Knobloch.

References

Amin, A. H., *et al.* (1954): *J. Physiol.* (*Lond.*), **126**, 596.
Armstrong, M. D., and Tyler, F. H. (1955): *J. clin. Invest.*, **34**, 565.
Balint, M. (1957): 'The Doctor, his Patient and the Illness', London.
Bowen, A., and Crane, C. B. (1958): 'York Mental Health Service, First Report, 1953-1957'.
Carse, J. (1959): 'The Worthing Experiment, January 1957 to December 1958': Report to the South West Metropolitan Regional Hospital Board.
Carstairs, G. M., *et al.* (1955): *Brit. J. prev. soc. Med.*, **9**, 187.

College of General Practitioners (1958): *Brit. med. J.*, **ii,** 585.
Cross, K. W., and Yates, J. (1961): *Lancet*, **i,** 989.
Eysenck, H. J. (1959): *J. ment. Sci.*, **105,** 61.
—— (1960): 'Behaviour Therapy and the Neuroses', London.
Foulds, G. (1958): *J. ment. Sci.*, **104,** 435.
Frohman, C. E., *et al.* (1960): *A.M.A. Arch. gen. Psychiat.*, **2,** 255.
——, *et al.* (1960) *Ibid.*, **2,** 263.
Heath, R. G., *et al.* (1958): *Amer. J. Psychiat.*, **114,** 917.
Horner, F. A., and Streamer, C. W. (1956): *J. Amer. med. Ass.*, **161,** 1628.
Jacobs, P., *et al.* (1959): *Lancet*, **i,** 710.
Jacobsen, E. (1960): Quoted in 'University of Cambridge Postgraduate Medical School Symposium on Depression. Preliminary Report', p. 18.
Joint Commission on Mental Illness and Health (1961): 'Action for Mental Health', New York.
Kessel, W. I. N. (1960): *Brit. J. prev. soc. Med.*, **14,** 16.
Kety, S. S. (1959): *Science*, **129,** 1528.
Kiloh, L. G., Child, J. P., and Latner, G. (1960): *J. ment. Sci.* , **106,** 1425.
Knobloch, H., and Pasamanick, B. (1959): *J. Amer. med. Ass.*, **170,** 1384.
Leach, B. E., *et al.* (1956): *A.M.A. Arch. Neurol. Psychiat.*, **76,** 635.
Lejeune, J., *et al.* (1959): *C.R. Acad. Sci. (Paris)*, **248,** 602.
Levine, M. (1942): 'Psychotherapy in Medical Practice', New York.
Lewis, A. (1960): *Amer. J. Psychiat.*, **117,** 289.
Logan, W. P. D., and Cushion, A. A. (1958): 'Studies on Medical and Population Subjects, No. 14', H.M. Stationery Office, London.
McGeer, P. L., *et al.* (1957): *J. nerv. ment. Dis.*, **125,** 166.
McKeown, T. (1958): *Lancet*, **i,** 701.
—— (1961): *Brit. med. J.*, **ii,** 166.
McLachlan, G. (1961): 'Report of the Conference on Psychiatric Epidemiological Research', London.
Macmillan, D. (1956): *Lancet*, **ii,** 1094.
—— (1960): *Ibid.*, **ii,** 1439.
Millbank Memorial Fund (1958): 'An Approach to the prevention of disability from chronic psychoses', New York.
Morrissey, J., and Sainsbury, P. (1959): *Proc. Roy. Soc. Med.*, **52,** 1061.
Norton, A. (1961): *Brit. med. J.*, **i,** 528.
O'Connor, N., and Tizard, J. (1957): 'The Social Problem of Mental Deficiency', London.
Osmond, H., and Smythies, J. (1952): *J. ment. Sci.*, **98,** 309.
Parkes, C. (1961): 'Community Care of Schizophrenics', in the press.
Pasamanick, B. (1959): *Amer. J. ment. Defic.*, **64,** 316.
—— *et al.* (1957): *Amer. J. publ. Hlth*, **47,** 923.
Rawnsley, K. (1960): 'Epidemiological Studies in Britain'. Memorandum submitted to the Medical Research Council Committee on the Epidemiology of Mental Disorders.
Registrar General (1953): 'Statistical Review of England and Wales, 1949. Supplement on Mental Health', H.M. Stationery Office, London.
Royal Commission on the Law Relating to Mental Illness and Mental Deficiency, 1954-57 (1957): H.M. Stationery Office, London.
Smythies, J. R. (1960): *Lancet*, **i,** 1287.
Tizard, J. (1961): Personal communication.
——, and Grad, J. (1961): 'The Mentally Handicapped and Their Families: A social survey', London.
Tooth, G., and Brooke, E. M. (1961): *Lancet*, **i,** 710.
Vogt, M. (1958): *Brit. med. J.*, **ii,** 965.
Wallace, H. E. R., and Whyte, M. B. H. (1959): *Ibid.*, **i,** 144.
Wing, J., *et al.* (1959): *Brit. J. prev. soc. Med.*, **13,** 145.
Witts, L. J. (1959): 'Medical Surveys and Clinical Trials', London.
Wolf, S. (1959): *Pharmacol. Rev.*, **11,** 689.
World Health Organization (1953): *Wld Hlth Org. techn. Rep. Ser. No.* **73.**

ADVANCES IN ORTHOPÆDICS

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The dilemma which faces the author of an article on advances in orthopædic surgery is to discern which of the techniques being constantly evolved will stand the test of time, for too often the successes of today become the failures of tomorrow. For this reason it is advisable to take a rather longer view of the developments in the specialty, and review some of the newer procedures which seem likely to have a permanent place in the orthopædic repertoire.

OSTEOARTHRITIS OF THE HIP

The surgical treatment of osteoarthritis of the hip is still the subject of much controversy; no operation has yet been devised which will give a high proportion of the patients lasting relief from pain and a useful range of movement in the hip. Most arthroplasties have proved disappointing; almost all tend to deteriorate in time and when both hips are involved there are few satisfactory and lasting results. Charnley (1961) has shown that synovial fluid is unable to lubricate steel or plastic which is in contact with bare bone, and in consequence friction causes abnormal wear of the prosthesis which replaces the head of the femur, and a resistance to movement which is often greater than the weakened muscles can overcome. In an endeavour to reduce the friction between metal and bone he devised a prosthesis to replace the head of the femur which bears against a polytetrafluorethylene socket which is implanted in the acetabulum. This arthroplasty has a low friction coefficient and the early results are much superior to any previous arthroplasty, but the method is too recent to make any final assessment of its permanent value.

In Great Britain high femoral osteotomy is now practised more often than any other operation. Osborne and Fahrni (1950), Adam and Spence (1958), Robins and Piggot (1960), and Nicoll and Holden (1961), have reviewed the late results of osteotomy. All agree that about 80 per cent. of patients derive lasting benefit from the operation, most of the unsatisfactory results being due to stiff hips and knees. Fibrous or bony ankylosis of the hip is liable to occur when there is less than 40° of flexion in the hip before operation, and a severe flexion contracture of the hip is also a contra-indication to osteotomy. Stiff knees can be prevented by the use of internal fixation instead of a plaster spica; this development has made the operation much less arduous for the elderly patient. At present it is usual to perform a femoral osteotomy when there is advanced joint destruction and in some of the patients there has been a partial restoration of the joint space and an improved range of movement. On these grounds Nissen (1960) has argued

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that earlier osteotomy might arrest the progress of the disease and give even better long-term results.

Arthrodesis is still the most satisfactory operation for a painful hip which has less than 40° of flexion, provided the opposite hip is not severely affected. Patients do not miss a small range of movement, and fusion is the most certain way of relieving pain. The 'V' arthrodesis of Brittain (1952) is relatively simple; it does not require a hip spica postoperatively, and is therefore very suitable for elderly patients.

None of the operations so far mentioned is suitable for severe bilateral osteoarthritis of the hip in an elderly patient. For these psoas tenotomy, or the so-called 'hanging hip' operation, is at present on trial. The principle of these two operations is similar, and is essentially a division of soft tissues which may include tendon of psoas, the adductor muscles close to their origin from the pelvis, the straight head of rectus femoris, and the attachment of gluteus medius to the great trochanter. The operation does not entail a prolonged period of postoperative treatment, for the patient is allowed up shortly after the wounds are healed. The relief of pain is probably due to abolishing to some extent the muscle spasm, and even if this is not permanent a relatively minor operation of this nature may be a useful addition to the procedures available for the treatment of this disabling condition.

FRACTURE OF THE NECK OF THE FEMUR

The number of fractures of the neck of the femur continues to rise year by year with the increasing age of the population. These fractures are often caused by trivial violence, and it has recently been shown that many of the victims have some degree of osteoporosis (Stevens *et al.*, 1961). These injuries present a considerable problem, especially the displaced intracapsular fracture.

Trueta and Harrison (1953) showed that the main vessels supplying the femoral head are the external epiphysial arteries which enter the upper part of the head close to the articular margin. These vessels are probably torn in most displaced subcapital fractures, and the viability of the head of the femur is then dependent on the vessels of the ligamentum teres. If the blood supply from this source is inadequate a part or the whole of the head of the femur will die; union of the fracture can then only occur by the slow process of creeping substitution (Phemister, 1940) which depends on new blood vessels crossing the fracture line and living trabeculæ being laid down on the surface of the dead trabeculæ which are then slowly absorbed. It is this process which gives the head of the femur the mottled and patchy increased density which is often incorrectly regarded as radiographic evidence of failure of union.

The difficulty in this fracture is to maintain contact and rigid fixation of the head and neck of the femur during the prolonged period required for bony union. It is more difficult to immobilize some fractures than others.

Comminution of the posterior cortex of the neck of the femur is common in the osteoporotic fractures; this predisposes to posterior rotation of the head of the femur, and if the fracture line is vertical there is a tendency for the head to resume its varus position. If the deformity recurs the new vessels crossing the fracture line will be ruptured, and non-union is inevitable.

In recent years many surgeons have become convinced that a Smith Petersen nail alone cannot immobilize the fracture adequately, and there has been a tendency to add a plate to the nail to secure better fixation to the

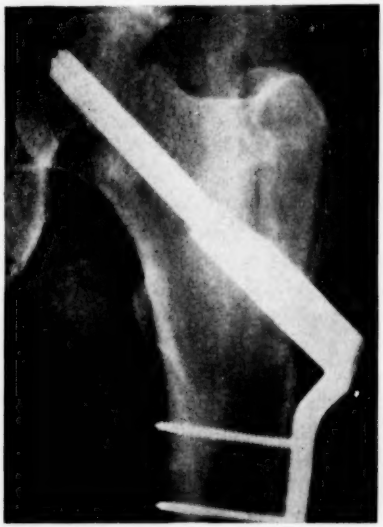

FIG. 1.—Sliding nail-plate as used for sub-capital fracture of the neck of the femur.

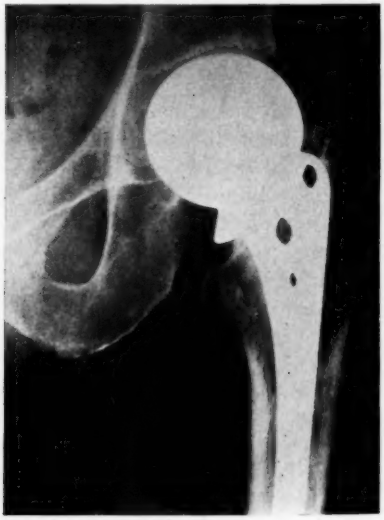

FIG. 2.—Fractured neck of femur: head fragment has been replaced by an Austin Moore prosthesis.

distal fragment (fig. 1). The fracture surfaces must be kept in contact throughout the period of union. Contact will be lost due to absorption of bone at the fracture surface unless a compression screw (Charnley *et al.*, 1957) or a sliding nail-plate (Brown, 1960) is used. With improved fixation it seems likely that a higher percentage of bony union will be secured, but there are always likely to be about 20 per cent. of failures due to total ischæmia of the head of the femur. For this reason many attempts have been made to determine whether the femoral head is viable in the first few days after injury. These methods have involved the use of radioactive tracers, and the injection of diodone into the head of the femur in an endeavour to demonstrate intact veins draining from it. None has proved reliable.

Dissatisfaction with the results of 'nailing' has caused many surgeons to adopt a primary replacement arthroplasty in elderly patients. This is a poor substitute for bony union of the fracture in a good position, but is justifiable in a patient who is not likely to impose a heavy strain on the prosthesis, and

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whose expectation of life is not more than a few years. A metal prosthesis with a long stem which is inserted into the medullary canal at the upper end of the shaft of the femur is the one most favoured (fig. 2). The head of the femur can be removed and the prosthesis inserted through a relatively small posterior approach which does not impose a greater strain on the patient than a 'nailing' operation. The patients are allowed to walk two weeks after the operation, and a prolonged period of rehabilitation is not necessary. The method is not devoid of complications and should be reserved for subcapital fractures or established non-union in the elderly or for those fractures in which it is impossible to obtain an acceptable reduction.

SURGERY OF RHEUMATOID ARTHRITIS

Until a few years ago surgery was seldom contemplated in the active phase of rheumatoid arthritis because of the risk of stirring up the disease. This may occur at any time in the first four to six weeks after operation when there is a fall in the postoperative concentration of corticosteroids, and can seriously affect the patient's ability to cooperate in the rehabilitation programme. Activity, however, may be suppressed temporarily by the administration of steroids, and is justified in a patient who is seriously crippled and for whom surgery offers the only possibility of resuming an independent existence.

The most fertile field for surgery is in the treatment of deformities of the wrist and hand. Snapping and locking of tendons is caused by rheumatic nodules in their substance, and rupture may occur due to invasion of the tendon by granulomatous tissue from the tendon sheath or neighbouring joint. The most disabling deformity is the ulnar deviation of the fingers which is caused by the deforming action of the extensor tendons when they slip to the ulnar side of the swollen and lax metacarpo-phalangeal joints. These deformities can be prevented by appropriate splinting in the early stages of the disease but it is also necessary to prevent the destructive effects of the granulation tissue on tendons and joints, and excision of this tissue is often advisable at a fairly early stage.

Full details of previous treatment must be obtained before operation. Prolonged steroid therapy may suppress the normal response of the adrenal glands to stress, which is by an increased secretion of cortisol, and death may occur during quite minor operative procedures from acute adrenal insufficiency. There is much individual variation in the effect of steroid therapy on the adrenal cortex but the production of adrenal hormones may be deficient for many months—possibly as long as two years—after steroids have been discontinued. For this reason it is desirable that all patients receiving steroids should be provided with a card or disc giving the details. Systemic steroid therapy must be continued before the operation, and supplemented by booster doses to cover the stress of the operation and anæsthetic. A dose of 100 to 200 mg. of hydrocortisone acetate should be given intramuscularly twenty-four hours before operation, and repeated

immediately before, and at the end of, the operation. Cortisone acetate, 50 mg. three times a day, or its equivalent, is given orally on the first day after operation and the dose is gradually reduced over the next week. It is important to appreciate that there is no harm in giving a patient steroids in excess of requirements to cover surgery. The risk of disaster lies in inadequate dosage.

Intra-articular injections of hydrocortisone have met with variable success. The immediate effect of the injection is often dramatic but the relief obtained is usually of short duration. Recently there have been reports of rapid deterioration of joints after repeated injections of hydrocortisone. This is probably caused by the patient over-exercising the diseased joint when the painful stimuli which normally inhibit movement are removed.

The cervical spine is involved in about one-third of the patients attending hospital with rheumatoid arthritis (Sharp, 1961). The disease affects both the apophysial joints and the intervertebral discs which are eroded by the vascular pannus. It may result in a fibrous or bony ankylosis of the affected vertebræ, or the joints may be destroyed and rendered unstable. Subluxation occurs at all levels but is more common at the atlanto-axial joint, and is best demonstrated in lateral radiographs of the cervical spine taken with the neck flexed and extended. In a small number of patients the subluxation may be sufficient to cause pressure on the spinal cord or medulla. The clinical picture is usually one of slowly progressive impairment of cord function, which may be followed by sudden onset of tetraplegia. The neurological disturbances are variable and may suggest a lesion at a higher level than the cervical cord. They are often overlooked initially in a patient who is severely crippled by rheumatoid arthritis. If there are signs of cord compression the subluxation should be reduced by skull traction, and a fusion performed of the unstable vertebræ. The operation should be considered even in neglected cases. Sharp (1961) reported excellent recovery of cord function after the operation, in a patient who had been completely tetraplegic for about thirteen months.

If the cervical spine is involved in rheumatoid arthritis the cord is vulnerable to injury when the patient is under general anæsthesia. Damage to the cord may occur during intubation of the trachea, or even when a patient is being lifted on to the operating table with the head unsupported (Barnes, 1961).

SURGERY OF BONE AND JOINT TUBERCULOSIS

Although bone and joint tuberculosis is becoming uncommon in Great Britain it is still a major problem in the underdeveloped countries and it is therefore interesting to reflect on the revolution in treatment that has occurred in the last decade. Until streptomycin became available the treatment of bone and joint tuberculosis was by 'rest, enforced, uninterrupted, and prolonged' under sanatorium conditions. The results of this treatment were far from satisfactory, almost a quarter of the patients admitted to hos-

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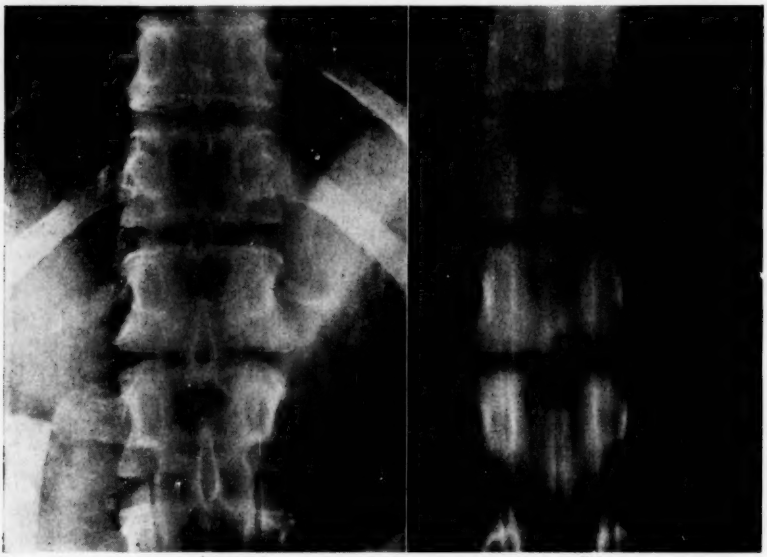
pital with tuberculosis of the spine died, and prolonged recumbency brought its own serious complications of renal calculi, premature fusion of the epiphyses, and severe shortening of the immobilized limbs. The immediate effects of the administration of streptomycin were not spectacular (Dobson, 1956) and until it was combined with a direct attack on the disease little progress was made.

The most important step in the cure of bone and joint tuberculosis is early diagnosis; this cannot be made on the clinical and radiographic



(a) (b)

FIG. 3.—(a) Antero-posterior x-ray of lumbar spine in a patient with early Pott's disease. There is narrowing of the intervertebral disc space between the first and second lumbar vertebræ. (b) Tomograph taken at same time as fig. 3a. This shows the presence of a para-discal abscess in the bodies of the first and second lumbar vertebræ.

appearances alone. Monarticular rheumatoid arthritis and villo-nodular synovitis of a large joint are often indistinguishable from synovial tuberculosis. Biopsy should always be performed on a joint which is painfully swollen or restricted in movement, and for which there is no obvious cause, which does not subside with a few weeks' conservative treatment. It is indefensible to delay the treatment of a tuberculous joint until the diagnosis is obvious. There is never any difficulty in obtaining healing of a biopsy wound if the patient is put on anti-tuberculous treatment immediately after the operation until the histological diagnosis is available. In the spine it is more difficult to achieve early diagnosis. Little abnormal may be seen on ordinary radiographs until there is considerable destruction of a vertebral body. Narrowing of a disc space or restriction of spinal movement in a patient who has no previous history of back pain are sufficient to justify

tomography (fig. 3). With modern techniques the dose of irradiation is not excessive and does not justify delay in establishing the diagnosis.

All patients with tuberculosis should for preference be admitted to an open-air hospital and given the standard anti-tuberculous drugs. In an adult the usual practice is to give 1 g. of streptomycin, 250 mg. of isoniazid and 12 g. of *para*-aminosalicylic acid (PAS) daily. When the patient leaves hospital the PAS and isoniazid are continued for a total period of twelve to eighteen months. Dihydrostreptomycin must be avoided: it can cause irrevocable deafness which may first be noticed days or weeks after the drug has been discontinued. Unfortunately, streptomycin also has a toxic effect on the vestibular portion of the eighth nerve but the patient is quickly aware of the disability and the vertigo usually subsides slowly when the drug is withdrawn.

The treatment of joint tuberculosis depends on the degree of destruction of the articular surfaces. If this is such as to prevent the restoration of a useful range of movement an arthrodesis should be performed at an early date. In this operation all accessible diseased tissue is excised so that reasonably healthy bony surfaces are brought into apposition. If, on the other hand, the disease is confined to the synovial membrane a good range of movement can be restored with conservative treatment which usually involves splinting until the erythrocyte sedimentation rate has fallen to normal levels and there are no clinical signs of activity; this may take from two to six months.

Many years ago Swett and his colleagues (1940) showed that a persistent abscess was the important factor in preventing the healing of Pott's disease. They recommended drainage of the abscess before the discovery of streptomycin, but this is even more important now, for a persistent abscess will prevent the attainment of a concentration of streptomycin which is lethal to *M. tuberculosis*. The present policy is therefore to drain a peri-spinal abscess and to remove radically all necrotic tissue as soon as the patient's condition permits. If a large gap remains after clearance of the diseased vertebræ it may be bridged by bone grafts; cancellous iliac bone is the most suitable but resected ribs may be used. The patient is nursed on a plaster bed before and after operation until the radiographs and sedimentation rate indicate that the disease is healing. A spinal fusion is seldom required, for spontaneous fusion of the diseased vertebræ often occurs after a radical clearance of the paravertebral abscess and all necrotic tissue.

CONGENITAL DISLOCATION OF THE HIP

'In a congenital dislocation of the hip we are confronted by a mechanical situation unusual in joint dislocations for we are here dealing with a dislocation which is intracapsular, and occurring in a joint in which there is an inherent flaw in its developmental make-up' (Platt, 1956).

If, however, the dislocation is detected and treated in the first few months of life the hip can be induced to develop normally as Putti (1927) demonstrated many years ago.

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The key to success is early diagnosis, and in Ortolani's (1948) sign we have a simple way of detecting dislocations in the newborn. If the limbs are abducted and externally rotated with the hips and knees flexed some resistance to this movement will be encountered on the dislocated side, and the head of the femur will be felt to slip in and out of the acetabulum with a characteristic click or clonk. Since 1952 all children born in the Malmo General Hospital have been examined for congenital dislocation of the hip by a pædiatrician within a few days of birth (von Rosen, 1957). The results have been remarkable, for no dislocation has been missed and by early diagnosis and three months' treatment on an abduction splint normal hips have been obtained in all children apart from the few in whom the dislocation did not conform to the standard pattern and was part of a generalized congenital joint disorder. In a routine examination of 6,700 newborn children Barlow (1961) reported that 47 children had a frank dislocation of one or both hips, and 41 others had unstable hips. More than half of these children were re-examined at 10 to 12 months of age and no dislocation was discovered which had been missed at birth. It is obvious that Ortolani's test should be made routinely on every child at birth, and those children in whom the test is positive should be referred immediately to an orthopædic surgeon for fuller investigation and treatment, for by so doing the problems that are inseparable from the treatment of congenital dislocation of the hip in older children would no longer arise.

References

Adam, A., and Spence, A. J. (1958): *J. Bone Jt Surg.*, **40B**, 219.
Barlow, T. G. (1961): Personal communication.
Barnes, R. (1961): *Proc. Roy. Soc. Med.*, **54**, 365.
Brittain, H. A. (1952): 'Architectural Principles in Arthrodesis', 2nd ed., Edinburgh.
Brown, J. T. (1960): Personal communication.
Charnley, J. (1961): 'Medical Orthopædic Symposium on Rheumatoid Arthritis', Empire Rheumatism Council, London, p. 53.
——, Blockey, N. J., and Purser, D. W. (1957): *J. Bone Jt Surg.*, **39B**, 45.
Dobson, J. (1956): In 'Modern Trends in Orthopædics' (Second Series), edited by Sir H. Platt, London, p. 65.
Nicoll, E. A., and Holden, N. T. (1961): *J. Bone Jt Surg.*, **43B**, 50.
Nissen, K. I. (1960): *Ibid.*, **42B**, 423.
Ortolani, M. (1948): 'La lussazione congenita dell'anca', Bologna.
Osborne, G. V., and Fahrni, W. H. (1950): *J. Bone Jt Surg.*, **32B**, 148.
Phemister, D. B. (1940): *A.M.A. Arch. Surg.*, **41**, 436.
Platt, H. (1956): 'Modern Trends in Orthopædics' (Second Series), London, p. 113.
Putti, V. (1927): *Arch. ital. Chir.*, **18**, 653.
Robins, R. H. C., and Piggot, J. (1960): *J. Bone Jt Surg.*, **42B**, 480.
Sharp, J. (1961): 'Medical Orthopædic Symposium on Rheumatoid Arthritis', Empire Rheumatism Council, London, p. 60.
Stevens, J., Freeman, P. A., Barnett, E., and Nordin, B. E. C. (1961): In the press.
Swett, P. P., Bennett, G. E., and Street, D. M. (1940): *J. Bone Jt Surg.*, **22**, 878.
Trueta, J., and Harrison, M. H. M. (1953): *Ibid.*, **35B**, 442.
von Rosen, S. (1957): *Acta orthop. scand.*, **26**, 136.

ADVANCES IN CARDIAC SURGERY

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During the past twenty years cardiac surgery has passed through three phases of development. The first was concerned with operations on the neighbouring great vessels. Closure of the patent ductus arteriosus by Gross (Gross and Hubbard, 1939), resection of coarctation of the aorta by Crafoord (Crafoord and Nylin, 1945), and systemic-pulmonary arterial anastomosis for the palliation of Fallot's tetralogy by Blalock (Blalock and Taussig, 1945) were surgical landmarks. These advances were followed by the introduction of operations carried out on the beating heart. Good examples were pulmonary valvotomy performed blindly through a right ventricular incision by Brock (1948) and Holmes Sellors (1948) and mitral commissurotomy by Bailey (1949). It was inevitable that the most striking advances could only follow the introduction of techniques which allowed visual intracardiac surgery.

VISUAL INTRACARDIAC SURGERY

This third surgical phase covers a period of less than ten years. Two fundamental and different problems face the surgeon. He must first develop a method involving surgery which will exclude the heart from the circulation while operations are carried out in a dry field within its cavities. During this time the patient must be protected from anoxia. The second problem concerns the correction of the individual cardiac lesion. It follows that the efficacy and the scope of intracardiac surgery will depend upon the efficiency and safety of the means used to protect the body during cardiac exclusion.

During the four years which have elapsed since Sir Russell Brock reviewed advances in cardiac surgery in *The Practitioner* (Brock, 1957), significant progress has been made in this direction. The techniques employed are complex enough to demand a large team which is trained in many disciplines. An extracorporeal circulation is usually employed and this implies the use of pumps and other apparatus which must be scrupulously maintained and skilfully used. The electrocardiogram and electroencephalogram are used to monitor changes in the heart and brain, and electrical manometers continuously record changes in blood pressure. Such observations are often made by the anæsthetist who is also responsible for the maintenance of an accurate blood balance. Frequent measurements are made of blood electrolyte and acid base changes and this, too, needs specialized knowledge and training. An extracorporeal circulation faces the hæmatologist with the problem of providing a large additional amount of specially

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prepared blood. This type of surgery can only be carried out successfully if it is based on thorough training in the experimental laboratory, where the talents of the physicist, the engineer and the chemist are joined to perfect the apparatus which will later be used on human patients.

If one adds to this formidable list of specialists the pædiatricians and cardiologists who select patients for operation after time-consuming investigations, it will be realized that the success of the cardiac surgeon depends upon the combined talents and special skills of a large number of colleagues. Modern research concentrates on increasing the safety of present methods and the invention of ways to reduce cardiac surgery to the size and simplicity of the average general surgical operation.

Open heart surgery may be carried out using hypothermia or the pump-oxygenator (heart-lung machine), or a combination of these techniques.

MODERATE HYPOTHERMIA

Circulatory arrest of three to four minutes' duration at normal body temperature produces irreversible cerebral damage and probable death. Bigelow (Bigelow *et al.*, 1950) showed that animals cooled to 20°C. by surface means could withstand circulatory standstill produced by clamping the venæ cavæ for as long as thirty minutes, because the brain requires less oxygen with a fall of temperature. The first successful clinical application of hypothermia was made by Lewis (Lewis and Taufic, 1953) in the closure of an atrial septal defect. It seemed to many that hypothermia, so easily induced by surface cooling of the anæsthetized patient, might provide the answer to the problem of creating the conditions for open heart surgery. Experience soon showed, however, that below 30°C. the human heart may develop irreversible ventricular fibrillation. The tolerance of the brain to circulatory standstill at this temperature is limited to only eight to ten minutes.

For this reason hypothermia induced by surface or veno-venous cooling, with temporary occlusion of the venæ cavæ to arrest the circulation, at present plays a minor role in cardiac surgery. It is almost entirely confined to the closure of the simple atrial septal defect due to a persistent ostium secundum, and to the relief of pulmonary valve stenosis in children. In the hands of experienced surgeons excellent results are obtained in carefully selected cases, but there is a tendency now to employ other methods which give more time for surgical correction and which allow for the unexpected difficulty and the occasional misdiagnosis.

CARDIOPULMONARY BYPASS USING A PUMP-OXYGENATOR

Bypass of the heart alone with perfusion of the lungs at normal body temperature is possible in the experimental laboratory but it is so difficult that its clinical use is not feasible. Bypass of both heart and lungs is surgically simple; it is achieved by exposing the heart, removing blood which returns

to the heart via cannulæ inserted into the venæ cavæ through the right atrium, and pumping this blood back to an appropriate systemic artery after it has passed through an artificial oxygenator. This idea was evolved long before the birth of thoracic surgery. The concept is simple but its successful application is the result of arduous experimental work over many years. The discovery of heparin, which is used to prevent the clotting of blood in an extracorporeal circulation, and the development of plastic materials which can be used in a pump-oxygenator, were events which have played a major part in the development of modern apparatus. It was fitting that in 1953, after many years of pioneer experimental work, Gibbon, of Philadelphia, became the first man to operate successfully within the human heart using cardiopulmonary bypass.

The apparent limitations of hypothermia were a spur to the development of many different types of pump-oxygenator. The difficulties of designing suitable pumps are few compared with the problems associated with the construction of an oxygenator capable of imitating the lungs. An artificial oxygenator contains an atmosphere of oxygen to which the blood is presented as the thinnest possible film in order to obtain the maximum amount of gaseous exchange. Oxygenators in current use rely on vertical stainless steel wire screens down which blood flows as a thin layer, or rotating discs on the surface of which filming takes place, or on the passage of a stream of oxygen bubbles through the blood, the bubbles being subsequently dissipated by passage through settling chambers and the use of silicone.

Blood is returned to the body through a cannula usually placed in the femoral artery pointing towards the heart. The aorta is perfused in retrograde fashion, the aortic valve if normal, remains closed, and a coronary circulation is maintained. Thus the heart continues to beat during cardiopulmonary bypass at normal body temperature. The cardiac cavities are not completely empty, because of the return of myocardial venous blood to the right atrium and bronchial venous blood mostly to the left atrium. In cases of Fallot's tetralogy, an increased bronchial circulation partially compensates for the obstruction to blood flow through the lungs, and as much as 25 per cent. of the cardiac output may pass through the bronchial circulation to the left atrium. It is now universal practice to insert a catheter into the left atrium, to apply suction and return the blood to the extracorporeal circulation. The combination of a moving heart and a continuous flow of coronary venous blood in the field of operation makes accurate surgery sometimes difficult.

ELECTIVE CARDIAC ARREST

The heart may be stopped by merely clamping the aorta above the coronary arteries, so-called anoxic arrest, or more rapidly by the injection of potassium citrate or acetylcholine into the root of the aorta just proximal to an aortic clamp. Whatever method is used the myocardium suffers damage from

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anoxia in proportion to the period of coronary occlusion. Fortunately, when the aortic clamp is removed and the myocardial circulation restored, the heart resumes a normal rhythm. Many surgeons now prefer to cool the heart either during general body hypothermia or by perfusion of the coronary arteries with cold blood, so that it is protected against long periods of anoxia.

Many cardiac surgical centres now use a pump oxygenator and cardio-pulmonary bypass with a heat exchanger in the extracorporeal circulation to produce varying degrees of total body hypothermia. As the patient cools, the metabolic demand for oxygen becomes less and this has prompted some workers to use low rates of perfusion and smaller oxygenators with a saving in the amount of blood needed to prime the apparatus. Hypothermia also protects the heart from anoxia during induced cardiac arrest and, depending upon the temperature, periods of complete circulatory standstill may be used if required during the intracardiac surgery.

PROFOUND HYPOTHERMIA

The limiting factor in surface cooling is the tendency of the heart to fail at a temperature below 30°C. If the function of the human heart is taken over by a mechanical heart in an extracorporeal circulation which includes a heat exchanger, it is possible to cool a patient to a very low temperature. During complete respiratory and circulatory arrest, surgery can be performed in a dry, still heart protected from anoxia by its own cold state. The circulation is then re-established and rewarming is carried out by the heat exchanger until the heart resumes normal rhythm. The extracorporeal circulation may then be gradually discontinued (Drew and Anderson, 1959; Drew, Keen and Benazon, 1959) and the cannulæ removed.

The surgical technique is not difficult to perform. The heart is exposed through a median sternotomy. A wide-bore stainless steel cannula is inserted into each atrium, usually through its appendage, and blood is allowed to drain into two reservoirs which may be regarded as extensions of the atrial chambers or as artificial atria. Blood from the left reservoir is then pumped through the heat exchanger into a cannula temporarily secured in the femoral artery while blood from the right reservoir is pumped into the pulmonary artery through a cannula inserted through a stab incision in the outflow tract of the right ventricle. An artificial systemic and pulmonary circulation can thus be established. The appropriate systemic flow is obtained by regulating the left pump, which determines the amount of blood returning to the right atrial reservoir. The right ventricular pump is then adjusted to keep the reservoir levels constant. At a nasopharyngeal temperature of 15°C., which closely corresponds to the temperature of the brain, the pumps are stopped. Clamps are placed on the venæ cavæ to prevent venous return to the heart and the latter is drained of blood through the atrial cannulæ.

At this temperature circulatory arrest has been proved safe for up to

fifty-five minutes, which is time enough for most operations. The brain may tolerate even longer periods but, if the intracardiac procedure is likely to exceed this time, it is carried out during two periods of circulatory standstill separated by perfusion lasting a few minutes. In this way two patients have survived 'suspended animation' lasting 78 and 82 minutes without harm.

The use of prolonged circulatory arrest in this way may have other applications and it has already been used successfully in at least two neurosurgical centres for the surgical treatment of inaccessible cerebral aneurysms.

The techniques which have been mentioned are applicable to a great variety of congenital and acquired heart lesions.

ACYANOTIC CONGENITAL HEART DISEASE

Septal defects.—A defect anywhere in the cardiac septum allows blood to flow across it from left to right because the pressures within the left atrium and left ventricle are higher than in the corresponding chambers on the right side of the heart. Pulmonary blood flow is increased and this imposes a burden on the heart proportional to the size of the shunt. When this is large operation is indicated, but small defects are compatible with long life and surgery is not required. In patients with pulmonary vascular disease causing a serious rise in pulmonary artery pressure, the shunt may be balanced or reversed from right to left causing cyanosis. Such cases are inoperable.

Atrial septal defect.—The patient with a simple atrial septal defect may not develop symptoms until adolescence or even later, and the condition is easy to miss in childhood because the murmurs are inconspicuous. Early operation is recommended because the risks of surgery are much greater in patients over the age of thirty. A less common but more dangerous variety of atrial septal defect is found low in the septum and is associated with an abnormality in the mitral or tricuspid valves producing incompetence. Symptoms usually occur early in life. The defect can be closed and the valve incompetence corrected. The results of surgery are not quite as good as for uncomplicated atrial septal defect because of the valve involvement, but the surgical mortality is less than 10 per cent.

Ventricular septal defect.—This is a more serious condition than an opening in the atrial septum. Many cases die in infancy from cardiac failure but medical treatment is often dramatically successful in controlling the failure and surgery can be performed at a later date. A patient with a loud murmur sometimes has a very small defect. The surgical mortality is 10 per cent. and becoming less and is mainly associated with heart block due to interference with the conducting bundle during suture of the defect. Until recently it was generally held that intracardiac surgery in children under the age of 2 years was contraindicated because of the high mortality. This attitude is now changing and it is hoped that very soon it will be pos-

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sible to salvage some at least of the 50 per cent. of cases of congenital heart disease who die in infancy. Provided that our techniques offer a reasonable chance of success there are good cardiological and sociological reasons why surgery should be carried out in this age-group.

CYANOTIC CONGENITAL HEART DISEASE

Transposition of the great vessels.—This is the most common congenital heart lesion producing cyanosis. Unless there is an accompanying septal defect or patent ductus arteriosus which allows mixing between the pulmonary and systemic circulation, the average expectation of life is less than six months. Most of those with a compensating defect die before the age of four years. Numerous operations have been devised for its correction. All have been unsuccessful except those which afford palliation only. There have been recent reports of apparent successes but there is at present no certain solution. The prognosis is so bad that it is justifiable to take any risk in an attempt to develop a successful procedure. This will ultimately be achieved.

Fallot's tetralogy.—The essential anatomical features of this malformation consist of a ventricular septal defect and pulmonary stenosis of varying severity. In the so-called acyanotic tetralogy the tendency for a left to right shunt across the defect is nicely balanced by the degree of pulmonary obstruction so that there may be no cyanosis except following strenuous exercise. At the other extreme is the deeply cyanosed patient with pulmonary obstruction so severe as to be almost complete. It is not surprising that a single standard operation may not be suitable in all cases.

The ideal is total correction of the abnormality but even in the best hands the mortality is 25 to 30 per cent., although this refers to cyanosed cases which are unselected. When the outflow tract remains small after resection of the obstruction, plastic inserts have been used to make it bigger. Controversy still continues as to whether the use of a foreign body in this situation is justified and whether the pulmonary incompetence produced by this manœuvre may not lead to disability later on. The critics favour a two-stage operation, attempting to correct the pulmonary obstruction at the first stage with suture of the defect at a later date. So far there is no certain evidence that this is a suitable alternative. Increasing collective experience should soon define the way in which these cases should be treated.

MITRAL STENOSIS

Mitral valvotomy is the most commonly performed of all cardiac operations and has become a routine procedure of proven value. It may seem surprising therefore to mention it in connexion with advances in cardiac surgery. For a long time the approach to the valve was through an opening made in the left atrial appendage and the commissures were separated either by finger fracture or the use of instruments of various designs. In a high proportion of

cases the results were beneficial and often dramatically successful, but in some patients symptoms recurred after a few years. This was due to re-stenosis in a few cases and to an inadequate operation in others.

A new technique for dealing with mitral stenosis described by Logan (Logan and Turner, 1959) enables a more complete valvotomy to be performed at no greater risk. The method consists of introducing an expanding dilator through a small incision in the apex of the left ventricle. The position of the instrument is checked by the index finger placed in the left atrium. When the head of the instrument expands, the dilating force within the contracted mitral orifice produces a split in the valve which in nearly every case follows the line of the commissures. This method has now been adopted by most cardiac centres in this country and there is little doubt that it produces a more effective valvotomy with little greater increase in the incidence of incompetence compared with the previous atrial approach. The diastolic murmur is often completely abolished but is sometimes replaced by a systolic apical murmur, which in most cases is consistent with an excellent final outcome.

In a few centres mitral valvotomy is being carried out under vision using cardio-pulmonary bypass. This method is more time-consuming and it is doubtful whether a better anatomical result can be obtained at the present time than by a blind transventricular approach. There may be a place for open mitral valvotomy in patients who have a history of multiple systemic emboli from thrombus formation in the left atrium and in patients with markedly calcified valves.

Unfortunately patients still present for surgery late in the course of the disease. The mortality following operation in patients who have symptoms due to mitral stenosis, who are below 40 years of age and who have not yet developed atrial fibrillation, is comparable with that for appendicectomy. With the onset of atrial fibrillation, and especially when there is a history of embolus, the risks are much higher. Mitral valvotomy is then always attended by the chance of cerebral embolus due to the dislodgement of a clot in the left atrium or its appendage during the operation. The use of anticoagulants and intermittent carotid occlusion during intracardiac manipulations may help to prevent this dreaded complication, but this does not apply to all cases.

AORTIC STENOSIS

Whereas congenital aortic stenosis in children can now be treated by open operation with a low mortality and good results, calcific aortic stenosis in adults presents more serious problems. Many sufferers from this disease live to old age, but when symptoms such as marked dyspnœa, angina pectoris and syncope occur the prognosis in the untreated case ranks with that of a malignant melanoma. The short time between the onset of symptoms and death means that many patients have little cardiac reserve with which to face aortic valvotomy. The closed operation through a blind

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transventricular approach has lost ground to the open operation using a cardiac exclusion technique.

A calcified, immobile, stenotic valve can be greatly improved without producing incompetence by commissurotomy and the careful removal of calcific nodules which are hindering the mobility of the cusps. It is necessary to approach the valve through an aortotomy and thus coronary circulatory arrest is obligatory. Such operations take a long time and are best done using hypothermia to protect the heart from anoxia.

MITRAL AND AORTIC INCOMPETENCE

In many ways the surgical problems are the same for both valves. The lesions can only be properly corrected by open heart surgery. If the condition is one of pure incompetence and the valve is not calcified, various plastic operations may be used on the cusps. The valve ring which is usually dilated may also be narrowed with advantage. It is unfortunate that an apparent cure of the condition is often followed by recurrence. The calcified predominantly incompetent valve presents one of the most difficult problems in cardiac surgery. The cusps are sometimes so destroyed that valve replacement would seem to be the only solution.

The design of valve prostheses is the subject of much research and many have already been used with promising immediate results, but foreign material embedded in the body has a poor reputation. Placed within the heart as a moving part one can but be hopeful but not prematurely enthusiastic over their use. When it is recalled that such a valve may move 40 million times in the course of the year, some idea can be obtained of the difficulties in designing and fitting a prosthesis which will not move from its position, act as a source of emboli due to clotting on its surface, or suffer mechanical breakdown.

CORONARY ARTERY DISEASE

There has been no recent dramatic advance in surgery for angina pectoris. Many different operations are used with success. Sympathectomy solely to relieve pain, the introduction of foreign substances, such as talc, into the pericardium in an attempt to improve intercoronary anastomoses, and the Vineberg procedure of implanting the bleeding internal mammary artery into the myocardium, have been the most widely used in recent years. All these operations have their critics and as the relief of pain is the only standard at present by which the operation may be judged, it is impossible to assess scientifically their effectiveness. Experience now allows such operations to be performed with a relatively low mortality and there is no doubt that they often produce relief from pain. The ideal case is one in which (a) pain is not sufficiently controlled by medical treatment to allow even light work; (b) the heart is small with no evidence of cardiac failure; (c) there is electrocardiographic evidence of increased ischæmia after exercise; (d) myocardial

infarction has not occurred during the previous six months. In such admittedly rare cases desperation is usually shared equally by the patient and his physician and both may derive benefit from surgery.

There have been sporadic reports of endarterectomy performed on occluded coronary arteries. Some have been done on the beating heart, others using an extracorporeal circulation with hypothermia to protect the myocardium while the arterial surgery was carried out. It is likely that endarterectomy offers better prospects than excision of the occluded segment or the use of a bypass graft. Unfortunately multiple occlusions are often present and after endarterectomy the reconstruction of the coronary vessels is extremely difficult. It is likely, however, that technical advances in the suture of small vessels will soon make surgery of these vessels a less hazardous procedure.

One notable advance is the ability of the radiologist to outline the coronary vessels with a radio-opaque medium. The most successful technique is that of Sones (Sones and Shirey, 1960). A catheter with a flexible tapered end which contains side holes is introduced via the brachial artery under radiographic control into each coronary ostium in turn. Dye is then injected rapidly into the vessel and cine-angiography is performed. This investigation promises to give much valuable information as to the extent and position of coronary occlusion and can be done with little risk even in patients with severe arterial disease.

References

Bailey, C. P. (1949): *Dis. Chest*, **15**, 377.
Bigelow, W. G., Lindsay, W. K., Harrison, R. C., Gordon, R. A., and Greenwood, W. F. (1950): *Amer. J. Physiol.*, **160**, 125.
Blalock, A., and Taussig, H. B. (1945): *J. Amer. med. Ass.*, **128**, 189.
Brock, R. C. (1948): *Brit. med. J.*, **1**, 1121.
—— (1957): *The Practitioner*, **179**, 435.
Crafoord, C., and Nylin, G. (1945): *J. thorac. Surg.*, **14**, 347.
Drew, C. E., and Anderson, I. M. (1959): *Lancet*, **i**, 748.
——, Keen, G., and Benazon, D. B. (1959): *Ibid.*, **i**, 745.
Gross, R. E., and Hubbard, J. P. (1939): *J. Amer. med. Ass.*, **112**, 729.
Lewis, F. J., and Taufic, M. (1953): *Surgery*, **33**, 52.
Logan, A., and Turner, R. (1959): *Lancet*, **ii**, 874.
Sellors, T. H. (1948): *Ibid.*, **i**, 988.
Sones, M. F., and Shirey, E. K. (1960): *Circulation*, **22**, 815.

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ADVANCES IN THE CHEMOTHERAPY OF MALIGNANT DISEASE

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THE field of cancer chemotherapy is burgeoning, as evidenced by the funds that are being made available for laboratory and clinical investigation, the number of publications and special conferences devoted to the subject, and the frequency with which physicians use chemotherapeutic agents and procedures in the management of various forms of cancer. In the United States during 1960, for example, the federal government allocated $21,538,000 to the Cancer Chemotherapy National Service Centre (CCNSC) to accelerate the search for chemicals for the control of cancer (National Health Education Committee, 1961). This has led to the synthesis of new drugs, the screening of thousands of compounds each year in laboratory animals, the pharmacological investigation of new classes of drugs, and the clinical trial of selected agents. To develop more reliable therapeutic assessments of new agents in man, cooperative clinical groups, using standardized therapeutic procedures and evaluation methods, have been established. By pooling their results, information concerning the practical value of a new drug or procedure can be rapidly accumulated on a large number of patients.

The CCNSC now publishes a journal presenting the results of independent and cooperative studies (*Cancer Chemotherapy Reports* 1959-1961) and a monthly survey of the world's literature (*Cancer Chemotherapy Abstracts* 1960-61). Under the ægis of the CCNSC, the report of a conference on experimental clinical cancer chemotherapy was published (Morrison, 1960) and, in collaboration with the CCNSC in many cases, the New York Academy of Sciences has published the proceedings of conferences on mercaptopurine (Rhoads, 1954), the alkylating agents (Karnofsky, 1958a), actinomycins (Waksman, 1960), and the use of screening methods (Stock, 1958). Separate major publications have appeared in several different languages (Clark, 1961; Estevez and Trimboli, 1960; Melli and Grifoni, 1960; and Diamond, 1958).

A MAJOR PROJECT

The search for anti-cancer drugs has become a major laboratory and medical project, and it is interesting to note that this great effort is being exerted, despite our poor understanding of the neoplastic process. The complexities of the therapeutic problem are extraordinary as can be illustrated by the varieties of cancer that occur in man, their different known and unknown causes, the numerous derangements in organ function which result from the growth of the disease, the biochemical differences among cancers of apparently similar histological type, and the development of

resistance in cancers previously sensitive to a chemotherapeutic agent. The urgent need for new and effective therapeutic methods, however, has created a militant spirit in chemotherapy research, and realistic obstacles, which might deter or divert more deliberate souls, are being circumvented or ignored in the vigorous drive for therapeutic success.

Meantime, we can assess here the advances that have been made recently as regards their use and value in the management of patients with non-resectable or disseminated neoplastic disease.

PROLONGATION OF LIFE

The most rigid criteria in evaluating an anti-cancer drug is prolongation of life, either by cure or control of the disease. Whilst a clinician may believe that the use of a drug has unquestionably prolonged life in an isolated case, the necessary demonstration of the efficacy of treatment is an increase in survival time in a statistically significant group of patients. This criterion has been met in only a few situations.

ACUTE LEUKÆMIA IN CHILDREN

With the introduction of the folic acid antagonists (methotrexate is most widely used), mercaptopurine and the adrenal steroids, such as prednisone, hæmatological remissions can be induced in about 80 per cent. of children with acute leukæmia. Burchenal and Ellison (1961) have shown that survival time has been increased from a median of five months to thirteen months by the use of these drugs, and about 10 per cent. of children survive more than two years. In the last five years there have been no substantial developments in the management of acute leukæmia. There is a recent report by Fernbach and his colleagues (1960), however, that cyclophosphamide can produce brief and usually partial hæmatological remissions in about 30 per cent. of children who have become refractory to other forms of treatment.

CARCINOMA OF THE PROSTATE

There is no doubt that surgical castration, œstrogen therapy or a combination of both, will cause remarkable remissions in 60 to 80 per cent. of cases of prostatic cancer, which may last for a number of years. Evidence has accumulated to indicate a significant prolongation of life (Nesbit and Baum, 1950). Adrenal steroids, adrenalectomy and hypophysectomy, while producing symptomatic relief in a few patients resistant to castration or œstrogen therapy, have not altered the course of the disease.

CHORIOCARCINOMA IN WOMEN

About 70 to 80 per cent. of women with metastatic choriocarcinoma have responded to intensive and repeated courses of methotrexate (Li, *et al.*, 1958) with tumour regression and decrease in chorionic hormone titre. Evidence of disease activity has not recurred thus far in about half of the patients who responded, and possibly some may be cured. Some of the

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patients in the other half of the group, who relapsed, have shown further responses to actinomycin D and a nitrogen mustard derivative (Li, 1961), and most recently to vinblastine (Hertz, *et al.*, 1960). Whilst adequate statistical studies are not complete, it seems reasonable to believe that methotrexate has prolonged life in choriocarcinoma in women. Since this tumour arises from the fœtal placenta, it is likely that immunological incompatibilities may exist between the cancer and the maternal tissues. This may explain the prolonged regressions in patients who respond to therapy, as well as the spontaneous regressions of the disease that have been observed (Bardawil and Toy, 1959).

PALLIATION, BUT UNCERTAIN EVIDENCE OF PROLONGATION OF LIFE

Drugs have been shown to produce regular evidence of temporary improvement in some types of cancer, but there is inadequate or negative statistical evidence that drug therapy has prolonged life.

WILMS' TUMOUR IN CHILDREN

This cancer of renal origin occurs principally in children. The metastatic disease was not highly responsive to drug therapy until the use of the actinomycins (Farber, *et al.*, 1956). Actinomycin D has been shown to produce temporary tumour regression in about 50 per cent. of cases (Tan, *et al.*, 1960), and the pulmonary metastases appear to be most sensitive to the drug. Remissions usually last for two to eight weeks, and further treatment may be effective in the responsive patient.

ACUTE LEUKÆMIA IN ADULTS

The remission rates produced by the adrenal steroids and mercaptopurine decrease progressively with the age of the patient; this has been attributed to the finding that acute lymphocytic leukæmia is far more common in children, and the myeloid variants dominate in older individuals. In young adults, 20 to 30 per cent. of patients may obtain temporary remissions with mercaptopurine or adrenal steroids; over 40 years of age, the response rate is less. Whilst methotrexate has been singularly ineffective in adolescence and beyond, remissions have been obtained in patients who have first responded and then become resistant to mercaptopurine (Ellison and Burchenal, 1957). There have been no recent developments in the chemotherapy of acute leukæmia in adults.

HODGKIN'S DISEASE AND LYMPHOSARCOMA

The clinical trial of a large number of polyfunctional alkylating agents and related compounds has continued in Hodgkin's disease and lymphosarcoma, but there is no convincing evidence that any derivative has shown an increased therapeutic index. By custom and convenience, intravenous nitrogen mustard (mustine) appears to be most useful in managing acute

problems (Karnofsky, 1958b), when therapy must be given rapidly, and chlorambucil is used most widely by mouth in ambulatory patients (Israels *et al.*, 1958; Karnofsky and Sykes, 1959). There is no satisfactory evidence that a patient refractory to an adequate trial of one type of alkylating agent will show a substantial therapeutic response to another derivative. The adrenal steroids have a minor role in advanced Hodgkin's disease, but in occasional patients with lymphosarcoma, adrenal steroids have produced prolonged control of the disease.

In the past year there has been considerable interest in vinblastine, an alkaloid extracted from the periwinkle plant (*Vinca rosea*) (Hodes *et al.*, 1960). This drug is generally given intravenously, and the usual dose is 0.1 to 0.15 mg./kg. (4 to 8 mg.) at weekly intervals; if there is no fall in the leucocyte or platelet count, the dose may be repeated. The drug may also be given by mouth, but the dosage is more difficult to control. Whilst there are occasional patients refractory to other forms of chemotherapy, who are temporarily benefited by vinblastine (Warwick *et al.*, 1960), sufficient clinical data are not yet available to recommend its use. In view of the fact that colchicine has been used to produce brief therapeutic responses in advanced Hodgkin's disease (Grollman *et al.*, 1955), it is of interest that vinblastine produces metaphase arrest in dividing cells, similar to colchicine (Cardinali *et al.*, 1961).

CHRONIC LEUKÆMIA

Chronic lymphatic leukæmia.—Chlorambucil and tretamine, administered cautiously, have been most widely used. They may produce prolonged hæmatological remissions, but it is recognized that without any treatment the disease may remain indolent and relatively benign for several years. In patients refractory to the alkylating agents, adrenal steroids, such as prednisone, may produce hæmatological responses, which can be maintained for several years by continued treatment. None of the antimetabolites has been useful in chronic lymphatic leukæmia.

Chronic myelocytic leukæmia.—Whilst a number of drugs will suppress the manifestations of chronic myelocytic leukæmia for long periods, there is no proof that the course of the disease is appreciably altered (Ellison and Burchenal, 1960). Busulphan is the most widely used alkylating agent, and mercaptopurine may be effective in patients who become resistant to busulphan.

There have been no appreciable advances in the management of *multiple myeloma*, *polycythæmia vera*, *mycosis fungoides* and *Kaposi's disease*. There is a recent report from Africa that mustine has produced prolonged remissions in Kaposi's disease (Cook, 1959), but in our experience, far-advanced Kaposi's disease has not been unusually susceptible to mustine.

OVARIAN AND UTERINE AND BREAST CANCER

Ovarian cancer.—Different alkylating agents, including tretamine (Sykes *et al.*, 1955), chlorambucil (Rundles *et al.*, 1958), and thiotepa (Bateman

and Winship, 1956) have been temporarily effective in about 30 per cent. of patients with advanced ovarian cancer. Regression of abdominal masses, ascites, œdema of the legs and pleural effusion has occurred. There has been renewed interest in the use of fluorouracil, an antimetabolite which interferes with pyrimidine metabolism (Heidelberger *et al.*, 1957). Temporary improvement has been reported in about 15 to 20 per cent. of adequately treated patients (Ellison, 1961).

Uterine cancer.—Kelley and Baker (1960) reported recently on the use of progesterone or its more active analogue, hydroxyprogesterone caproate, in metastatic endometrial carcinoma. Of 15 cases treated, five showed excellent and prolonged responses; of those responding, four had regression of pulmonary metastases whilst one showed regression of local disease. The usual dose of hydroxyprogesterone caproate is 500 mg. twice weekly intramuscularly, and treatment should be continued for at least two to three months. The treatment has a sound endocrine basis, in that progesterone will inhibit the proliferative stage of the normal endometrium, and certain endometrial carcinomas may retain some of the hormonal responsiveness of their tissue of origin. More extensive trials of progestational agents in metastatic endometrial carcinoma are now under way.

Breast cancer.—There have been no recent advances in the management of breast cancer, and techniques of altering the hormonal status of the patient by the addition of steroid hormones, or by the ablation of endocrine glands, remain the principal systematic procedures for treating metastatic disease. Fluorouracil (Curreri *et al.*, 1958) and thiotepa (Bateman, 1958) have been stated to produce a high incidence of remissions in breast cancer, but these reports are not consistent with the findings of others (Ellison, 1961; Karnofsky, 1958a).

TESTICULAR TUMOURS

Seminomas have an excellent prognosis and the metastatic disease is also sensitive to radiotherapy and alkylating agents. The embryonal and teratocarcinomal choriocarcinomas in the male are far more malignant, and generally resistant to chemotherapy. Recently, Li and his colleagues (1960) have reported that a combination of the oral administration of methotrexate, 5 mg., and chlorambucil, 10 mg./day, with interrupted five-day courses of actinomycin D (0.5 mg/day x 5), given until signs of toxicity to the bone marrow or digestive tract appear, would produce remissions in 35 per cent. of patients with metastases from carcinomas of the testes, and in the responsive patients elevated urinary gonadotrophin titres decreased substantially or to normal levels. Ten of 28 patients showed complete disappearance of metastatic disease for varying periods; three of these have remained free of disease for approximately two years.

ADRENAL CARCINOMAS

In the rare functional carcinomas of the adrenal cortex, 11-hydroxy and 17-ketosteroid production is increased, and the patient may develop a

Cushingoid appearance. It has been shown, in the past two years, that o,p'DDD [2,2-bis(4-chlorophenyl, 2-chlorophenyl)-1, 1-dichloroethane)] will inhibit adrenal steroid synthesis, relieve the Cushingoid signs and symptoms, and occasionally produce tumour regression (Bergenstal *et al.*, 1959, 1960). The drug is given orally; the dose is gradually raised to 10 g./day, and then reduced to a tolerated level. Toxic effects are anorexia, nausea and vomiting, cutaneous reactions, somnolence and adrenal insufficiency.

CARCINOMA OF THE LUNG

The alkylating agents have produced temporary regression of pulmonary and metastatic lesions in about 30 per cent. of the treated cases, and they have been particularly effective in the superior vena cava compression syndrome (Golbey, 1961). In our experience, mustine intravenously has given the most rapid response, but other types of alkylating agents have been advocated. In statistically controlled studies, mustine may have caused a very slight prolongation of life. It is important to note that in these same studies the use of cortisone was associated with decreased survival as compared with the untreated controls (Wolf *et al.*, 1960).

CARCINOMA OF THE LARGE BOWEL

Fluorouracil has been given intravenously in metastatic large bowel cancer (Ansfield and Curreri, 1959). The reported response rate varies greatly among different clinics: from 8 to 41 per cent. (Ellison, 1961). In our experience the response rate, based on objective and subjective improvement for a period of one month or longer, is close to 10 per cent. The recommended dose of 15 mg./kg. intravenously for three successive days, and then 7.5 mg./kg. is given on alternate days until signs of toxicity appear. Fluorouracil toxicity, consisting of oral and intestinal lesions, and bone marrow depression may be extremely severe, and it may first appear several days after a course of treatment is completed. An appreciable mortality and morbidity rate can be expected, in the range of 5 to 10 per cent., if fluorouracil is used in adequate doses.

MISCELLANEOUS CARCINOMAS

There are no reports indicating consistent benefit from anti-cancer drugs against the other major forms of cancer. Fluorouracil has been used in carcinoma of the stomach, pancreas and liver with isolated reports of benefit; the various alkylating agents have been tried in cancer of the head and neck, œsophagus, stomach, kidney and cervix uteri, and in melanomas, with rare suggestions of clinical benefit. The triple combination of methotrexate, actinomycin D and chlorambucil (Li, 1961) has been used with occasional temporary regressions in metastatic soft-part tumours. Vinblastine has been studied in a variety of cancers, with inconclusive results (Moore and Watne, 1961a; Frei *et al.*, 1961).

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CONTROL OF EFFUSIONS AND INTRATHECAL CHEMOTHERAPY

Control of effusions.—The alkylating agents have been given intrapleurally for the control of recurrent effusions, and Weisberger (1958) reports that about 64 per cent. of the effusions are diminished or controlled. These results appear to be equal to those obtained with local use of radioactive agents. The fluorinated pyrimidines have sometimes been useful in controlling effusions (Ellison, 1961), and recently Gellhorn and his colleagues (1961) have controlled pleural and abdominal effusions by the introduction of mepacrine into the effusion fluid.

Intrathecal chemotherapy.—Methotrexate does not penetrate well into the cerebrospinal fluid following parenteral administration, and leukæmic cells may proliferate in the central nervous system of patients whose systemic disease is under control on chemotherapy. In these circumstances, intrathecal methotrexate has been successful in the treatment of meningeal involvement (Whiteside *et al.*, 1958).

CLINICAL INVESTIGATIONS INVOLVING SPECIAL CHEMOTHERAPEUTIC PROCEDURES

Because of the narrow therapeutic index of most anti-cancer drugs, a variety of stratagems is being tried in order to enhance the tumour-inhibiting activity and to diminish the systemic toxicity of a drug. So far, these clinical procedures have been mainly experimental, and there is insufficient evidence to support their general use.

ISOLATION PERFUSION

Creech and his colleagues (1959) developed the isolation perfusion method, whereby the blood supply to a cancer-bearing area is temporarily occluded, and the occluded area is perfused by means of pumps. This method will maintain a high circulating concentration of the drug in the involved area while excluding the drug from the systemic circulation. It has been feasible to perfuse an area for about sixty minutes before returning it to the systemic circulation (Clarkson and Lawrence, 1961). The problems of leakage of the perfusate into the systemic circulation and chemical damage to the perfused tissue have complicated the procedure. Mustine, phenylalanine mustard and thiotepa have been used most extensively, but actinomycin D, methotrexate, fluorouracil and other compounds have also been used. The areas perfused include the extremities, pelvis, liver, lungs, face and brain. Whilst prolonged remissions have been reported, they are not frequent and the drug of choice and the indications for the procedure have not been established.

INTRA-ARTERIAL INFUSIONS

In order to concentrate the anti-cancer drug in a tumour-bearing area, it has been injected, according to several dose schedules, into arteries supplying these areas. Mustine has been most commonly used, and occasional, but

not very substantial, benefit was obtained (Krakoff and Sullivan, 1958). Sullivan and his colleagues (1959) described a technique whereby methotrexate was given by continuous infusion into the external carotid artery for carcinoma in the facial region, and folinic acid, an antidote of methotrexate, was given intramuscularly to counteract the systemic toxicity of methotrexate. Remarkable local regressions, including disappearance of all evidence of disease, occurred, although in the majority of cases the cancer extended beyond the area supplied by the infused artery, and an incomplete regression was obtained. There is no doubt that selective injury to the cancer can be produced by this method, which has also been used in the hypogastric arteries for carcinoma of the pelvic region with results similar to those obtained in the head and neck cancers (Sullivan *et al.*, 1960a). The hepatic artery has been catheterized, and prolonged local methotrexate infusion with systemic folinic acid injection, as well as other drugs, used against metastatic cancer to the liver (Clarkson *et al.*, 1961): the technical procedures and complications associated with this method have been described by Duff and his colleagues (1961). Other chemotherapeutic agents, such as iododeoxyuridine and the fluorinated pyrimidines have been infused, with occasional, but not substantial, therapeutic results. The practical applications of the continuous local infusion method are not established.

DOSAGE VARIATIONS

Because of rate differences in the pattern of metabolism between normal and neoplastic proliferating cells, there is the possibility that altering the dosage schedule in the administration of an anti-cancer drug may increase the adverse effect on cancer cells while decreasing its toxicity to normal tissues. Fluorouracil was shown to be considerably less toxic when given by continuous intravenous administration (Sullivan *et al.*, 1960b; Lemon, 1960), whereas fluorodeoxyuridine showed a 30-fold increase in toxicity by continuous infusion (Sullivan *et al.*, 1960b). Methotrexate is also appreciably more toxic by continuous infusion. Whilst variations in dose schedules are under study, there is, as yet, no acceptable clinical evidence that one can dissociate the systemic toxicity of a drug and its anti-cancer activity by oral or intravenous administration.

BONE MARROW PROTECTION

Bone marrow injury is generally the limiting factor in determining the dosage of an anti-cancer drug that can be administered safely. Several procedures are now under clinical investigation in the hope of protecting the bone marrow, so that larger doses of an anti-cancer agent will be tolerated by the patient.

Extremity tourniquets.—The simplest method has been the use of extremity tourniquets, applied high on the extremities during, and for four to ten minutes after, the intravenous injection of mustine (Conrad and Crosby, 1960). The degree of protection in adults is uncertain, but it is

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not great (Schilling *et al.*, 1961); somewhat better evidence of protection of the bone marrow of the extremities by tourniquets was obtained in children, in whom the peripheral marrow is normally more cellular.

Mid-torso occlusion.—A more drastic method is to occlude temporarily the blood supply to the lower half of the body while, and for a few minutes after, mustine is injected into an arm vein. This has been accomplished by introducing a balloon-type catheter from the femoral artery into the aorta and placing the balloon at the level of the diaphragm; at the same time, an inflatable belt is placed around the patient's abdomen. Both are inflated above arterial pressure, the injection is given, and the occlusion is released ten minutes later (Miller and Lawrence, 1961). Whilst this method will protect the pelvic bone marrow against doses of 1 mg./kg. or more of mustine, and prevent the serious hæmatological disturbance ordinarily produced by this dose of mustine, a new complication has been neurological disturbances, apparently due to large doses of mustine. Other types of rapidly reactive alkylating agents, without the neurotoxic effects of mustine, are now under study.

Miscellaneous methods of bone-marrow protection.—Pre-treatment of the patient with adrenaline has been reported to decrease the bone-marrow depressant effect of mustine (Field, 1961). Bierman and his colleagues (1961) have performed leukaphereses in order to produce a hyperplastic bone marrow before mustine therapy, and they have been able to administer larger than conventional doses without severe hæmatological complications. Bone marrow has been withdrawn from the patient before the injection of mustine, and returned intravenously twenty to thirty minutes later in order to populate the damaged bone marrow area (Black *et al.*, 1959).

COMBINATION OF CHEMOTHERAPEUTIC AGENTS AND X-RAYS

There is continuing interest in the possibility of sensitizing cancer cells to radiation by the use of a chemotherapeutic agent. It has been asserted that 'synkavit' (Mitchell, 1948), fluorouracil (Hall *et al.*, 1960) and actinomycin D (Farber *et al.*, 1960) will enhance the effects of radiation. Whilst an additive effect of the two agents is evident when the cancer is responsive to both agents, there is no satisfactory evidence that potentiation of radiotherapy effects has been produced by chemotherapy. Hyman and Reese (1956) have reported that tretamine in combination with radiotherapy will reduce the dose of x-rays necessary to control retinoblastoma. Recently, Djordjevic and Szybalski (1960) have reported that iododeoxyuridine, which is incorporated into deoxyribonucleic acid, will sensitize cells growing in tissue culture against radiation.

PROPHYLACTIC USE OF ALKYLATING AGENTS

There are laboratory data indicating that treatment with an alkylating agent will prevent the formation of metastases following the intravenous injection

of tumour cells in the rat (McDonald *et al.*, 1957). In numerous studies, an alkylating agent, such as mustine or thiotepa, has been given immediately after the removal of a potentially curable cancer, in order to reduce the possibility of cancer cells, liberated during surgery, establishing metastases. Controlled cooperative studies have been conducted by the CCNSC in cancers originating in the female breast, colon and rectum, stomach, lung and ovary. Thus far, the most interesting results have been obtained in breast cancer treated prophylactically with thiotepa. Two schedules were used: 0.2 mg./kg. on the day of surgery and repeated for either three or two days postoperatively. According to the most recent report 43 per cent. of the untreated patients and 24 per cent. of the thiotepa patients (0.8 mg./kg. total) have recurrent disease after twenty-four months. In the second schedule (0.6 mg./kg. total) which has been used for a shorter time, the recurrence rate is 20 per cent. and 14 per cent. for the untreated and treated groups, respectively (Moore and Watne, 1961b). These results are being followed with great interest.

CLINICAL EVALUATION OF NEW ANTI-CANCER DRUGS

As a result of the great screening effort for anti-cancer drugs, there is a continuous flow of new agents for clinical evaluation. Some of these agents, after a brief clinical study, may be widely reported, although there is neither substantial evidence of therapeutic value nor proof of unique activity as compared with agents already available. Whilst conservative interpretations of clinical reports are justified by experience, new and hopeful contributions to cancer chemotherapy may be expected from such a screening programme.

Polyfunctional alkylating agents.—Various analogues of the several classes of alkylating agents, which have special properties in terms of dosage, tolerance by oral administration, and diminished or absent acute pharmacological effects, all depress bone marrow and exhibit a similar spectrum of therapeutic activity at equivalent levels of host toxicity (Karnofsky, 1958a). Larionov (1961) has suggested, however, that phenylalanine mustard is particularly effective in seminoma, ovarian cancer and multiple myeloma, and a large number of derivatives has been prepared in the hope of obtaining a more specific compound. Other alkylating agents under study include 'urethane mustard', also referred to as a 'dual antagonist' (Thurman *et al.*, (1961), 'uracil mustard' (Shanbrom *et al.*, 1960), and tretamine (Schulze, 1957; Rochlin and Shiner, 1961). A compound, possibly acting as an alkylating agent, is 1,4-bis(3-bromopropionyl)piperazine (A-8103) (Mrazek and Economou, 1961), and it is now under clinical investigation.

Antimetabolites.—Many derivatives of the folic acid antagonists, the purine derivatives (Burchenal, 1956) and the fluorinated pyrimidines (Ellison, 1961) have been studied in man, with no evidence of unique therapeutic activity over the prototype compound. Iododeoxyuridine is a drug of great interest (Welch and Prusoff, 1960), but has shown no practical anti-cancer activity, and 6-azauridine (Welch *et al.*, 1960), whilst it caused

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transient regression in leukæmia, is of limited value. The latter drug is of biochemical interest, in that it has been shown to block the decarboxylation of orotidine, and thus prevent the contribution of orotidine to pyrimidine metabolism. Azaserine (Ellison *et al.*, 1954) and 6-diazo-5-oxo-L-norleucine (Magill *et al.*, 1957), which are glutamine antagonists, although exerting transient therapeutic effects in Hodgkin's disease and in the hypercalcæmia of breast cancer have not proved to be of practical value. Azaserine, in combination with mercaptopurine, appeared to prolong hæmatological remissions in some children with acute leukæmia, but the results have not been striking enough to recommend the addition of azaserine (Heyn *et al.*, 1960).

Antibiotics.—Antibiotics are being screened intensively for anti-cancer activity, and several compounds, active in laboratory animals, have reached clinical trial. The actinomycin derivatives studied appear to have no substantial advantage over actinomycin D in man (Waksman, 1960). Mitomycin C, a Japanese antibiotic (Sukigara *et al.* 1957; Jones, 1959), is an active anti-cancer drug, but its therapeutic spectrum seems to parallel the alkylating agents. In our experience, however, its effects are less consistent than the alkylating agents, and adequate dosage is more difficult to regulate. Streptonigrin is a highly toxic antibiotic which also produces severe bone-marrow depression in man (Hackethal *et al.*, 1961). The tolerated dose in the adult is between 1 and 2 mg., which makes it the most active chemical bone-marrow depressant known. It has produced brief remissions in Hodgkin's disease, but the drug appears to be too hazardous to use in relation to its limited therapeutic activity.

SUMMARY

Slow progress is being made in the search for anti-cancer drugs. In the past two years definite advances are seen in the confirmed value of methotrexate in choriocarcinoma in females, the use of progestational hormones in endometrial carcinoma, actinomycin D in Wilms' tumour in children and the triple combination of actinomycin D, methotrexate and chlorambucil in testicular cancer. Less certain achievements are the effects of cyclophosphamide in inducing remissions in acute leukæmia in children, temporary improvement from vinblastine in advanced lymphomatous disease, and the use of o,p'DDD in functional carcinomas of the adrenal cortex.

New techniques are under study to enhance the effects of available drugs: by using the alkylating agents prophylactically to prevent metastases at the time of operation of breast cancer, by the isolation perfusion of cancer-bearing areas with drugs, and by the continuous arterial infusion of methotrexate to a tumour-bearing area, while protecting the host by the systemic administration of folinic acid. Various methods are being tried to protect the bone marrow against anti-cancer drugs, so that larger doses can be given, and the use of drugs to sensitize tumours to radiation. These projects, while of scientific interest, have not been established in practice.

A number of new drugs, including many analogues of conventional drugs,

are being studied in man. This vast effort, which involves preclinical and pharmacological study as well as clinical trial and evaluation of many drugs against the major forms of cancer, will lead to the discoveries that will increase our ability to alleviate and control some of the varied and numerous manifestations of cancer in man.

The work reported in this article was supported by research grants from the American Cancer Society, the Damon Runyon Memorial Fund for Medical Research, the Lasker Foundation, New York, and by Grant CY3215 from the National Cancer Institute, Public Health Service, Bethesda, Maryland.

References

Ansfield, F. J., and Curreri, A. R. (1959): *J. nat. Cancer Inst.*, **22**, 497.
Bardawil, W. A., and Toy, B. L. (1959): *Ann. N.Y. Acad. Sci.*, **80**, 197.
Bateman, J. C. (1958): *Ibid.*, **68**, 1057.
——, and Winship, T. (1956): *Surg. Gynec. Obstet.*, **102**, 347.
Bergenstal, D. M., *et al.* (1959): *Trans. Ass. Amer. Phycns.*, **72**, 341.
——, ——, ——, —— (1960): In 'Biological Activities of Steroids in Relation to Cancer', ed. by G. Pincus, and E. P. Vollmer, London, p. 463.
Bierman, H. R., *et al.* (1961): *Blood*, **17**, 303.
Black, M. M., Speer, F. D., and Stone, M. L. (1959): *Ann. intern. Med.*, **51**, 517.
Burchenal, J. H. (1956): In 'Current Research in Cancer Chemotherapy', Cancer Chemotherapy National Service Centre, Bethesda, Maryland, p. 1.
——, and Ellison, R. R. (1961): *Clin. Pharmacol. Ther.*, **2**, 523.
Cardinali, G., *et al.* (1961): *Proc. Amer. Ass. Cancer Res.*, **3**, 215.
Clark, R. L., Jr. (1961): 'Cancer Chemotherapy', Springfield, Illinois.
Clarkson, B., and Lawrence, W., Jr. (1961): *Med. Clin. N. Amer.*, **45**, 689.
——, *et al.* (1961): *Proc. Amer. Ass. Cancer Res.*, **3**, 216.
Conrad, M. E., and Crosby, W. H. (1960): *Blood*, **16**, 1089.
Cook, J. (1959): *Lancet*, **ii**, 25.
Creech, O., Jr., *et al.* (1959): *J. Amer. med. Ass.*, **169**, 339.
Curreri, A. R., *et al.* (1958): *Cancer Res.*, **18**, 478.
Diamond, H. D. (1958): 'The Medical Management of Cancer', New York and London.
Djordjevic, B., and Szybalski, W. (1960): *J. exp. Med.*, **112**, 509.
Duff, J. K., *et al.* (1961): *Cancer*, **14**, 744.
Ellison, R. R. (1961): *Med. Clin. N. Amer.*, **45**, 677.
——, and Burchenal, J. H. (1957): *J. chron. Dis.*, **6**, 421.
——, —— (1960): *Clin. Pharmacol. & Ther.*, **1**, 631.
——, *et al.* (1954): *Cancer*, **7**, 801.
Estevez, R. A., and Trimboli, O. de E. (1960): 'Quimioterapia Antiblastica', Books I, II, Buenos Aires.
Farber, S., *et al.* (1960): *Ann. N.Y. Acad. Sci.*, **89**, 421.
——, Toch, R., Sears, E. M., and Pinkel, D. (1956): *Advanc. Cancer Res.*, **4**, 1.
Fernbach, D. J., *et al.* (1960): *Cancer Chemother. Rep.*, **8**, 102.
Field, J. B. (1961): *Proc. Amer. Ass. Cancer Res.*, **3**, 224.
Frei, E., *et al.* (1961): *Cancer Chemother. Rep.*, **12**, 125.
Gellhorn, A., *et al.* (1961): *Dis. Chest*, **39**, 165.
Golbey, R. B. (1961): *Med. Clin. N. Amer.*, **45**, 627.
Grollman, A., *et al.* (1955): *Ann. intern. Med.*, **42**, 154.
Hackethal, C. A., *et al.* (1961): *Antibiot. and Chemother.*, **11**, 178.
Hall, B. E., *et al.* (1960): *Lancet*, **i**, 115.
Heidelberger, C., *et al.* (1957): *Nature* (*Lond.*), **179**, 663.
Hertz, R., *et al.* (1960): *Proc. Amer. Ass. Cancer Res.*, **3**, 118.
Heyn, R. M., *et al.* (1960), *Blood*, **15**, 350.
Hodes, M. E., Rohn, R. J., and Bond, W. H. (1960): *Cancer Res.*, **20**, 1041.
Hyman, G. A., and Reese, A. B. (1956): *J. Amer. med. Ass.*, **162**, 1368.
Israels, L. G., *et al.* (1958): *Ann. N.Y. Acad. Sci.*, **68**, 915.

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Jones, R., Jr. (1959): *Cancer Chemother. Rep.*, **2**, 3.
Karnofsky, D. A. (1958a): *Ann. N.Y. Acad. Sci.*, **68**, 657.
—— (1958b): *Ibid.*, **68**, 899.
——, and Sykes, M. P. (1959): In 'Cancer', ed. by R. W. Raven, London, vol. 6, p. 41.
Kelley, R. M., and Baker, W. H. (1960): In 'Biological Activities of Steroids in Relation to Cancer', ed. by G. Pincus, and E. P. Vollmer, New York and London, p. 427.
Krakoff, I. H., and Sullivan, R. D. (1958): *Ann. intern. Med.*, **48**, 839.
Larionov, L. F. (1961): *Cancer Chemother. Rep.*, **11**, 165.
Lemon, H. M. (1960): *Ibid.*, **8**, 97.
Li, M. C. (1961): *Med. Clin. N. Amer.*, **45**, 661.
——, Hertz, R., and Bergenstal, D.M. (1958): *New Engl. J. Med.*, **259**, 66.
——, *et al.* (1960): *J. Amer. med. Ass.*, **174**, 291.
McDonald, G. O., *et al.* (1957): *Ann. Surg.*, **145**, 624.
Magill, G. B., *et al.* (1957): *Cancer*, **10**, 1138.
Melli, G., and Grifoni, V. (1960): 'Terapia delle Emoblastosi', Rome.
Miller, D. G., and Lawrence, W., Jr. (1961): *Proc. Amer. Ass. Cancer Res.*, **3**, 251.
Mitchell, J. S. (1948): *Brit. J. Cancer*, **2**, 351.
Moore, G. E., and Watne, A. L. (1961a): *Cancer Chemother. Rep.*, **12**, 192.
——, —— (1961b): *N.Y. St. J. Med.*, **61**, 2417.
Morrison, B. H., III (1960): 'Conference on Experimental Clinical Cancer Chemotherapy', National Cancer Institute Monograph No. 3, Washington, D.C.
Mrazek, R. G., and Economou, S. G. (1961): *Cancer Chemother. Rep.*, **12**, 51.
National Health Education Committee, Inc. (1961): 'Facts on the Major Killing and Crippling Diseases in the United States Today', New York, p. 10.
Nesbit, R. M., and Baum, W. C. (1950): *J. Amer. med. Ass.*, **143**, 1317.
Rhoads, C. P. (1954): *Ann. N.Y. Acad. Sci.*, **60**, 183.
Rochlin, D. B., and Shiner, J. (1961): *Cancer Chemother. Rep.*, **11**, 69.
Rundles, R. W., Coonrad, E. V., and Willard, N. L. (1958): *Ann. N.Y. Acad. Sci.*, **68**, 926.
Schilling, A., *et al.* (1961): *Proc. Amer. Ass. Cancer Res.*, **3**, 265.
Schulze, W. (1957): *Dtsch. med. Wschr.*, **82**, 1465.
Shanbrom, E., *et al.* (1960): *J. Amer. med. Ass.*, **174**, 1702.
Stock, C. C. (1958): *Ann. N.Y. Acad. Sci.*, **76**, 409.
Sukigara, K., Takeishi, T., and Noguchi, T. (1957): *Chemotherapy*, **5**, 323.
Sullivan, R. D., Miller, E., and Sykes, M. P. (1959): *Cancer*, **12**, 1248.
——, *et al.* (1960a): *Cancer Chemother. Rep.*, **10**, 39.
——, *et al.* (1960b): *Ibid.*, **8**, 77.
Sykes, M. P., *et al.* (1955): *Surg. Gynec. Obstet.*, **101**, 133.
Tan, C. T. C., *et al.* (1960): *Ann. N.Y. Acad. Sci.*, **89**, 426.
Thurman, W. G., *et al.* (1961): *Cancer Chemother. Rep.*, **12**, 105.
Waksman, S. A. (1960): *Ann N.Y. Acad. Sci.*, **89**, 283.
Warwick, O. H., *et al.* (1960): *Cancer Res.*, **20**, 1032.
Weisberger, A. S. (1958): *Ann. N.Y. Acad. Sci.*, **68**, 1091.
Welch, A. D., *et al.* (1960): *Cancer Chemother. Rep.*, **9**, 39.
——, and Prusoff, W. H. (1960): *Ibid.*, **6**, 29.
Whiteside, J. A., *et al.* (1958): *A.M.A. Arch. intern. Med.*, **101**, 279.
Wolf, J., *et al.* (1960): In 'Biological Activities of Steroids in Relation to Cancer' ed. by G. Pincus, and E. P. Vollmer, New York and London, p. 413.

ADVANCES IN PREVENTIVE MEDICINE

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'Preventive Medicine is the medicine of the future.'

THE Osler dictum has been somewhat in the discard during the last twenty years—due, no doubt, to the dazzling triumphs of the chemotherapeutic age. The prospect of a 'sure-cure shot' of antibiotic seemed to be so much more certain of success than the time-taking and troublesome care inevitably required by preventive procedures. Today, however, there is a new and real interest in prevention, and a growing belief that it is more likely to live up to its old reputation of being 'better than cure'; it is also usually pleasanter, cheaper—and much more certain. Best of all, there is growing recognition, as has been implicit always in the work of good practitioners that preventive and curative medicine are complementary, and that prevention includes not only avoiding the disease altogether when possible, but also the secondary and important aspects of prevention—the limitation of complications and of the ultimate disorders and disabilities which might result. In other words, preventive medicine constitutes a large part of the daily duty of a family doctor.

IMMUNIZATION

The example which comes readily to mind nowadays of methods of primary prevention is that of vaccination and immunization. It is trite to speak of the triumphs which have been won in the field of the prevention of diphtheria, whooping-cough, and poliomyelitis. A local example will suffice.

Fifty years ago in this city there were over one hundred deaths every year from diphtheria. Over a hundred beds in the 'fever hospital' were often in use for diphtheria cases alone. There were anything from forty to a hundred deaths from whooping-cough every year, whereas nowadays there have been no deaths from either diphtheria or whooping-cough for several years.

In England and Wales during the past quarter of a century deaths from diseases such as diphtheria and whooping-cough which previously caused the deaths of some 5000 children annually have been reduced to a combined total of much less than 50.

The list of diseases against which effective protection is available is now impressive: smallpox, diphtheria, whooping-cough, tetanus, tuberculosis, poliomyelitis—to name only those of real importance in this country. Moreover, it is a gradually growing list, and I, for one, believe there is a case for adding influenza vaccine, for use in chronic bronchitics and other vulnerable patients, despite the coldness of the Cohen Committee's recent verdict of 'not proven'.

POLIOMYELITIS IMMUNIZATION

One example may be selected for brief discussion: the increasingly weighty case for poliomyelitis immunization. The risk of paralytic poliomyelitis has become greater recently, due partly (despite public opinion to the contrary) to the improved living conditions of the people and the higher standards of hygiene resulting in the less frequent subclinical infections which stimulate greater immunity. There seems no doubt that protection with a killed vaccine of the Salk type is about 70 per cent. to 85 per cent. effective—a remarkable achievement.

The best system of dosage appears to be an interval of one month between the first and second injections, and not less than six months between the second and third injections, but there is no doubt that we shall have to face the prospect of injections every few years in view of the need for improving and maintaining immunity in the absence of subclinical infections. The fourth dose is now a well-established procedure in British schoolchildren and six are recommended in the United States.

It seems particularly important to protect all pregnant women, not only because they appear to be peculiarly prone to paralytic poliomyelitis, but also to ensure that some measure of immunity may be passed over to the baby. Such protection may be of great value in the first few months of life, tiding over the time until active immunization is begun. A standard practice is now two doses between seven and ten months, and the third at eighteen months. Such a practice has the additional advantage that the (very slight) chance of provocation paralysis from other immunizing procedures against whooping-cough and diphtheria will be lessened.

At the present time the vaccine is available for all up to 40 and (what is often forgotten) for special groups, such as practitioners, dentists, nurses—inside or outside hospital—and assistants, and their immediate families. The continuing and almost complete lack of reactions following poliomyelitis vaccine administration is a most welcome feature.

The prospect of an attenuated *live* vaccine is an exciting one by reason of its apparent safety. Over a hundred million doses have been given in various parts of the world, and by reason of its extraordinary simplicity of administration in a sweet or on a lump of sugar, cheapness, and the possibility of greater and longer immunity it appears to have a great future. Until the final relative merits of the live and killed vaccines are established, there is no doubt that the public are accepting the idea of primary prevention of disease more and more through the success of poliomyelitis vaccination.

IMPROVING THE PHYSICAL ENVIRONMENT

Equally important in many respects are the advances which have been made in modifying the physical environment, which is a direct and primary procedure in preventive medicine, by removing or lessening environmental evils such as dirty air, dirty water, milk and food, and slum housing. It is

a platitudinous but none the less imperative principle of preventive medicine that we must make the surroundings and circumstances of man favourable to health—to promote and to enhance health—rather than to allow an unfavourable environment to harm health and to cause disease directly or indirectly. The sanitary disposal of refuse and excreta, the eradication or control of infestation by vermin and other pests are traditional but ever-new examples of the safeguarding of the health of the individual and the community, for those 'in the know' well realize the breakdowns (and breakthroughs) of the sanitary barriers against infection which may often occur.

SOCIAL PATHOLOGY

It is the total environment, however, that must be improved in order to meet the needs of man. A significant change in thinking has been the recognition of the multi-factorial causation of poor health.

Some bronchitic patients I have been studying recently, almost without exception lived in defective and/or inadequate houses in overcrowded streets with little opportunity for healthy play—breathing polluted air at home, sometimes at work, and often in their recreations in 'pubs and clubs'. Nearly all had a long history of infections and illnesses, with diets for long inadequate in first-class protein and in protective fruit and vegetables with their important mineral and vitamin content. They all smoked: some very heavily.

Social pathology has seldom a single cause, hence there is need for a 'total' outlook today as well as for a wider provision of preventive procedures. The cause of the illness is so often a complex of causes; let it be noted that if the causes are many, there is often a greater opportunity for attack by all the members of the team: the family doctor, public health inspector, health visitor, district nurse, home help, as well as the medical officer of health and other workers in the health and social services. As there are many possible contributory causes of common chronic illness, measures may be taken in the modern practice of preventive medicine by intervening and interrupting the many chains of circumstance which bind the individual to ill-health and preclude the fulfilment of his potential for full and effective living. It is not practicable, or often necessary, to attempt to eradicate all the many possible causes of an illness. Alleviation, if nothing more, may sometimes be obtained by removal of a single cause.

Harmful health and social factors may be modified by effective health and social measures. This may come about not only by better housing, cleaner air and safer food, but also by improvement of the psychological environment which affects the lives of people greatly. Much illness is caused by unhappiness, and health depends much more upon happiness than happiness does on health. In my area a health advice bureau, marriage guidance, and other 'personal' health services are in operation. Greater understanding of the psychological make-up of people leads to less likelihood of anxiety and maladjustment. Various forms of group therapy, informal and attractive methods of health education, and improved social and recreational activities can provide a means whereby men and women can

learn to understand the influences which make for physical and psychological health.

PREVENTIVE MEDICINE AND MENTAL SUBNORMALITY

In an as yet small, but unmistakably increasing, number of cases, a preventable cause of mental subnormality is found; such causes may operate before, during, or after birth. Congenital syphilis has long been known as a preventable cause of a small proportion of mentally defective children, but with the practice of preventive public health procedures such as antenatal screening as well as antibiotic treatment, this cause has been removed from the list of pressing problems facing the public health worker. Now, however, there is good evidence that virus infections (rubella almost certainly, and other viruses possibly) in early pregnancy may cause mental deficiency. Every pregnant woman definitely exposed to rubella in the early weeks of pregnancy can have an injection of gamma globulin provided freely by the Public Health Laboratory Service.

There is also suggestive evidence that a woman suffering other illness and perhaps even severe emotional disturbance during pregnancy has a greater tendency to produce defective children. Toxæmia of pregnancy and rhesus factor antibodies may act directly in the production of kernicterus and brain damage. A severe birth injury can without doubt cause a mental defect; prematurity, which can be associated with both of these, is an important predisposing factor to birth injury. The prevention of premature, precipitate, prolonged, or difficult labour is a field in which better obstetrical and midwifery care has recently made a great contribution.

A most promising aspect of subnormality emerges from an investigation of phenylketonuria. Although it is not a common condition, it is of great importance because of the general principle involved that an inborn error of amino-acid metabolism can cause mental subnormality, and that this error is detectable by a simple urine (ferric chloride) test. The screening of all babies from the fourth week of life for phenylketonuria is carried out by more than one local authority by means of such testing of all babies born in their area, or attending welfare clinics, and especially those babies or children referred for ascertainment of mental defect. The importance of this early detection of phenylketonuria lies in the fact that cases have been recorded in which a modification of diet has led to definite improvement in the intelligence.

Phenylketonuria is but one example of the prospects that are opening up of prevention in the field of mental abnormality. Certain other defects associated with metabolism of amino-acids may well repay careful study and reference for clinical investigation and treatment. In addition, there are many other diseases due to faulty metabolism or disordered endocrine mechanism, such as cretinism, Wilson's disease, galactosæmia, and hypoglycæmia. The reduction or elimination of meningitis due to the meningococcus, or to tuberculosis, are also important points of attack on this difficult problem.

OTHER MEASURES FOR PREVENTIVE AFTER-CARE

Re-housing in one-floor accommodation. The absence of stairs and the cleaner air, whether it is in a top-storey flat or an overspill area, have meant in my experience added health and employment as well as relief from distress and disablement for the patient and his family.

Appropriate employment.—Disablement resettlement officers of the Ministry of Labour give great help in advising and securing appropriate employment, in attendance at rehabilitation centres and in providing training for more suitable trades or employment, perhaps under sheltered conditions. It must be admitted that the difficulties in retraining older men of low morale are great. Nevertheless, some patients have been enabled to live healthier, happier, and more useful lives, avoiding the heavy social, financial and psychological cost of chronic absenteeism and unemployment.

Health education.—In view of the association of heavy cigarette smoking with chronic bronchitis it follows that renewed effort must be made, particularly among schoolchildren—perhaps even the 'seniors' in the primary school—to encourage children not to start smoking or, if it has started, for it to cease forthwith. Attractive, comprehensive, and persistent personal health education will be required. In Salford, a club on the lines of 'smokers anonymous' has been formed in order to encourage those who wish to give up smoking, but have so far failed to do so, to try again. The techniques of discussion and group therapy have been used at weekly evening meetings held at the health department. It is suggested that effort is well worth while to secure cessation of smoking in a few and a reduction to below the danger level of twenty cigarettes a day in many.

Clean air.—Remarkable but perhaps unspectacular progress has been made in cleaning the air. Several urban areas in the country can record a reduction in pollution both from smoke and sulphur fumes by 10 per cent. to 30 per cent. in the last few years. The white collar of the urban worker remains white longer nowadays!

THE ROLE OF THE GENERAL PRACTITIONER

One of the most significant advances which has been made recently is the ready acceptance by a growing number of general practitioners of their role in preventive medicine, which is certainly not the prerogative of public health personnel—it is the job of every one of us. The National Health Service is the greatest single opportunity for the practice of preventive medicine ever known, and the family doctor is at the centre of the whole structure. His work is essentially one of home care; the provision of appropriate facilities to help in home care is an important function of his ally, the medical officer of health. Furthermore, a growing proportion of family doctors have a real interest in, and knowledge of, the principles and practice of preventive medicine, and are in a supreme and unique strategical position to give authoritative advice on the promotion of physical and mental health and the prevention of disease.

ADVANCES IN INDUSTRIAL MEDICINE

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TWENTY-FIVE years ago the Association of Industrial Medical Officers, which does not contain all the doctors who work in the field of industrial medicine, possessed only 20 members. Last year its total membership was 1,038. The difference between these two figures is a dramatic summary of the advancing interest in industrial medicine. About a book a year is published on this subject in Great Britain, and its academic representation has increased since the war to three professorial university departments—at Newcastle upon Tyne, Manchester and London—together with a number of lecturers at other medical schools. In recent years the Minister of Labour has provided himself with an Industrial Health Advisory Committee, over which he personally presides. This body is doing valuable work in generally promoting the subject and in directing the attention of employers to where they can obtain advice. Before the last general election one of the political parties published a manifesto which included a plan for a national industrial health service. This is the general background of increasing interest against which the subject is now practised.

CLINICAL

It is by no means realized by every medical man that industrial diseases are relatively uncommon (Ministry of Labour, 1960a). Leaving out industrial pulmonary disease, about 1000 cases are certified each year, and notwithstanding the rising level of background enlightenment this figure has remained roughly constant for the last forty years. Some diseases, such as lead poisoning, have greatly diminished, whilst others, such as epitheliomatous ulceration from tar, pitch, oil or chrome, have increased. Lead poisoning is now almost unknown in painters and printers, except in the minds of medical students who are taking their final examination. Lead, the more powerful poison, has excited a more powerful preventive response than have the insidiously slow-acting carcinogens in tar, pitch and oil, but it may well be wondered how many of these epitheliomas would still appear to be so, if sectioned and viewed with a microscope.

INDUSTRIAL PULMONARY DISEASE

Industrial pulmonary disease (Gilson, 1960) is still the main clinical problem in this field of medicine; for example, in 1958 there were about four times as many cases of industrial pulmonary disease diagnosed as all the other

industrial diseases put together. In mineral dust pneumoconiosis an international system of radiological classification has been developed which enables the x-ray appearance to be converted into a shorthand formula, employing letters and numerals. The success of this method depends upon good radiology, experienced viewers who know what they are looking at, and a set of films of standard appearances to be studied in the early stages of the technique. It is also as well to realize that there are differences between observers' opinions, and between the opinions of the same observer at different times. Newell and Browne (1955) showed that the symptoms of coal-miners' pneumoconiosis bore no relation to the radiological picture, but that they became worse as the men became older. More recently, Cochrane and his colleagues (1961) have objectively confirmed this finding by demonstrating that ventilatory function, measured by a physiological test, is independent of the radiological picture even in progressive massive fibrosis until there is more than 20 sq. cm. of shadow on the radiograph. Therapy in pneumoconiosis remains restricted. Ramsay and his colleagues (1959), using anti-tuberculous drugs, were able to bring about some clinical improvement in cases of progressive massive fibrosis complicated by open tuberculosis, and they were also able to convert the sputum from positive to negative. There was, however, very little radiological change. McCallum (1960) found anti-tuberculous therapy ineffective in sputum-negative progressive massive fibrosis.

During the past few years the cotton-dust dyspnœa of byssinosis has received a good deal of attention, and it has been shown (Roach and Schilling, 1960) that it is the larger dust particles which are the more important, whereas it is the smaller in mineral-dust pneumoconiosis. The chest tightness in byssinosis seems to be a pharmacological phenomenon related to a possible protein in the cotton fibre which may act by liberating histamine (Bouhuys *et al.*, 1960). Cotton workers appear to be safe from the disease if the weight of cotton in the air is less than 100 mg. per 100 cubic metres, and efforts are now being made to reduce the dust concentration to as near this figure as possible with an exhaust extraction device applied to the dustiest points of the carding engine.

There has been some recent advance in our knowledge of asbestosis, in that it has been shown that a low vital capacity accompanies the fibrosis of the lungs in these men. From this follows the suggestion that measurement of the vital capacity should be done regularly in asbestos workers and that a diminution, greater than that likely to be due to increasing age, should suggest the onset of the disease. The early x-ray appearances in this disease are even more debatable than they are in a mineral pneumoconiosis, and a breathing test may well prove both more sensitive and more satisfactory. In coal-dust pneumoconiosis the lungs are only a little stiffer than normal, but they are much stiffer (Leathart, 1960) in asbestosis, and the negative pressure or 'pull' needed in the trachea to draw in a given volume of air is greater (fig. 1).

LEAD POISONING

There is now a method of treating lead poisoning which is really effective (Shiels *et al.*, 1956). This is to give sodium calcium edetate, 60 mg. per kg. body weight daily for four days by mouth. A still more rapid effect can be produced by giving the same dose, dissolved in half a litre of normal saline, by intravenous drip, running it in slowly over several hours. This can be repeated, if necessary, every day for not more than three days, to form a course. After four days without treatment the whole course can be repeated if there has been no clinical improvement or increased urinary excretion of lead. But even two intravenous infusions of this dose can produce dramatic improvement as demonstrated (fig. 2) in the case of a young lead smelter recently seen by the writer. If possible, before treatment is started a 24-hour specimen of urine must be passed into a lead-free flask or polythene bottle and a sample estimated for lead. This should be done for each twenty-four hours of treatment and for a few periods afterwards. Reliability is greatest where a trained nursing staff is familiar with collecting 24-hour urinary specimens and the laboratory with estimating the lead in them. The progress of the patient should be assessed by considering the clinical and chemical situations together.

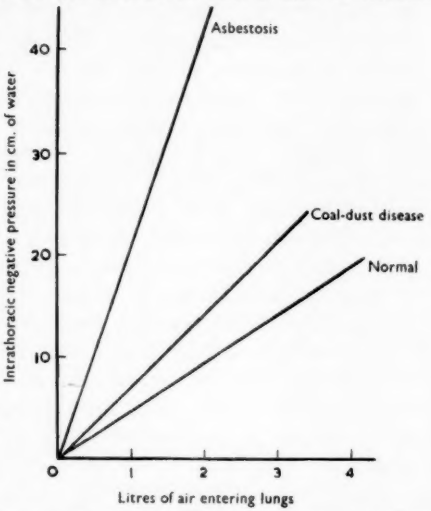

FIG. 1.—The intrathoracic negative pressure or 'pull' which is needed to draw air into the lungs is greatly increased in asbestosis. It is only slightly greater than normal in coalminers' pneumoconiosis.

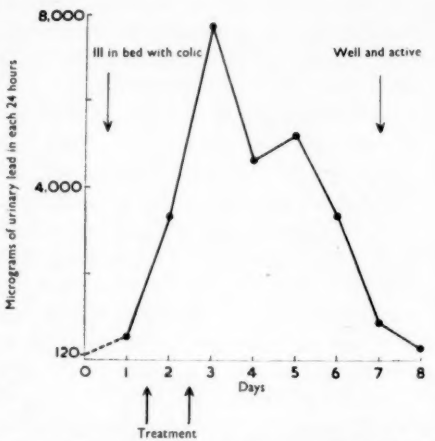

FIG. 2.—Treatment by two intravenous infusions of 60 mg./kg. body weight of sodium calcium edetate causes a dramatic rise in urinary lead excretion, coupled with clinical improvement.

It is not certain from the available evidence whether metallic lead lodged in the body is likely to be absorbed and cause poisoning, and the following case seen in the Newcastle department bears upon this point:

A young farmer lost his right forearm and part of his arm in a shooting accident. Some months after the accident he was perfectly well clinically, but it was estimated that the stump of the arm (fig. 3) contained nearly an ounce (30 g.) of lead-shot with a surface area of about 7 square inches (45 square centimetres). Analysis of his urine for lead, however, showed that he was only excreting less than half the normally accepted amount. Neither was the amount of coproporphyrin in the urine raised as it usually is in lead absorption.

This new drug, however, must not be given to lead workers prophylactically—and for two important reasons: first, so doing will distract attention from the improvement of the working environment which is essential to prevent the disease, and secondly, other metals, including the all-important iron, may well be leached out of the body by it.

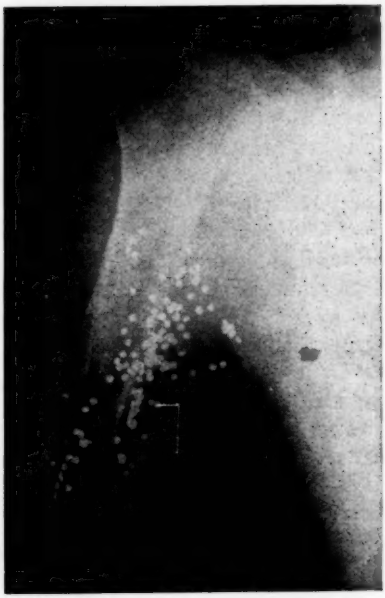

FIG. 3.—There is nearly an ounce (30 g.) of lead shot with a surface area of about 7 square inches in the stump of this farmer's arm.

SYNTHETIC RESINS

During the last war a range of most powerful synthetic resins and adhesives was developed. These have become used more and more extensively, particularly in the electrical engineering industry, and also for bonding moulded fibreglass and in the manufacture of synthetic boarding. They are known as the epoxide resins, and are often used in small factories which are unfamiliar with the care which is necessary in handling hazardous substances. Moreover, factories of this type are apt to employ economic labour which is not too hygiene-minded. Skin eruptions, conjunctivitis, and irritation of the respiratory tract if there are fumes, are apt to follow the use of these substances. These effects can only be prevented by carefully avoiding contact with the resin and by providing exhaust extraction ventilation to lead away any fumes which may arise from working with hot material (Grandjean, 1957).

ACCIDENT NEUROSIS

The troublesome problem of 'accident neurosis' has recently had new light shed upon it (Miller, 1961). It was shown as long ago as the 1914-18 War that this condition was more likely to follow a trivial injury, or even none at all, than a bad physical injury, and it now seems clear that under the conditions of modern industrial life it is related to the hope of financial

gain from compensation. Accident neurosis is a function of poor personal morale and its incidence can be diminished by active, optimistic encouragement on the part of the patient's doctor from the start. The minds of these patients need directing towards the idea of a rapid return to earning their living. Whilst speed of decision is very effective in clearing up the condition, a not unimportant social element in the etiology is that accident compensation, like claims against hospitals, is paid from public funds—and these are large.

GASES IN RESUSCITATION

The relative efficacy of oxygen or carbogen (oxygen + 5 per cent. carbon dioxide) in resuscitation has become an important issue in the last few years, and now that the sounds of the scientific controversy have died down, it may be useful to suggest what line should be taken by the doctor who works in the practical situation in industry (Lane and Dingwall-Fordyce, 1960). The first point to consider is the probable cause of the industrial asphyxia which may be encountered; for example, in steel foundries or among main-laying gangs in the gas industry, it is likely to be due to carbon monoxide. On the other hand, in the electrical industry electrocution is the potential danger, but in some cases it may not be possible to say which hazard is the more likely.

If there is a definite risk of poisoning by carbon monoxide it is better to have available cylinders containing a mixture of oxygen and 5 per cent. carbon dioxide, because it has been reasonably well shown by scientific experiment that such a mixture eliminates carbon monoxide from the blood more quickly than does oxygen alone. If, however, there is no such risk, pure oxygen should be provided and it is, perhaps, better to provide only this for industries where the cause of the asphyxia cannot be definitely foreseen. It is probably not wise to provide both, and then to lay upon the first-aid man the responsibility of deciding which to use in the rough-and-tumble of an emergency situation.

ARTIFICIAL RESPIRATION

There are three important types of men concerned with the subject of artificial respiration: the enthusiastic promoter (often from abroad) of the latest method; the white-coated physiologist working under carefully controlled conditions in his laboratory; and the first-aid man suddenly called to respire artificially one of his mates who is clothed in greasy dungarees and is slumped unconscious over a pipe in a dark and awkward corner of the works. The first-aid man, and the situation in which he works in practice, is the member of this trio who merits most consideration. He is professionally conservative and not used to the changing fashions of medical practice. Moreover, he tends to follow the book and puts great weight on the immutable truth of the printed word, but he is the man who has to do the job in the emergency situation.

Some years ago the Holger Nielsen method replaced the Schafer, and now the expired air, or mouth-to-mouth, technique is becoming a rival to the Holger Nielsen. From the physiological point of view, it is clear that the tidal volume of air which can be moved in the subject is greater in the expired air method, and that the Holger Nielsen only produces adequate ventilation in the hands of experienced operators upon subjects with healthy elastic chests.

Should therefore the expired air method now be generally introduced? Physiological opinion is clear, but what of the field worker? The natural revulsion to blowing into the mouth of a dead-looking victim is strong, and this causes a reluctance to be trained. Recovering cases are not unknown to vomit. Operators become dizzy from hyperventilation and there is a little risk of pulmonary overdistension in the subject. Some of these field disadvantages can be overcome—or can seem to be overcome: for example, a small hand bellows can be used as a ventilator. But are these likely to be at hand when the accident happens? Speed in starting is the most important, and if the first few minutes are lost, so may be the patient. Nothing deteriorates so quickly as apparatus which is seldom used. An airway can be used to avoid contact of the lips, but it must be inserted with a dexterity and gentleness not always possessed by a man trained as a mechanical fitter or manual worker. The natural objections to training with the use of live subjects can be overcome by using a dummy or manikin.

This method of artificial respiration is gaining ground at the present time, and what is needed now is some experience under practical field conditions. It is not possible to perform a 'controlled experiment' in the scientist's sense of the phrase in these circumstances, but such well-reported experience will help to decide whether there should be a general change from the Holger Nielsen to the expired air method of artificial respiration. At the present time this decision should, perhaps, remain open.

BARRIER CREAMS

Most of us are a little panacea-minded, and we look for a one-shot method of dealing with a condition which can often be prevented by general care. The relation of 'barrier' creams to 'industrial' dermatitis is a topical example of this situation. It is often not certain whether a case of 'industrial' dermatitis is, in fact, due to the working environment, and it is even less certain that a barrier cream would have prevented it. It is clear, however, that the most important way to avoid irritation of the skin by a material at work (e.g. oil) is to fit a mechanical barrier to the machine in the form of a splash guard, or to the human being in the form of a glove. In greasy fitter's work neither of these measures may be possible and a disciplined system of hand care must be taught to the men and to the management. One such method, using hydrous lanolin (hydrous wool fat B.P.) which has proved reasonably effective, has been taught to a group of fitters who were given the following written instructions:—

(1) Before starting work: rub lanolin well into fingers, hands and forearms.
(2) Before lunch: wash hands with soap and water. Dry on towel.
(3) Before work: rub in lanolin again.
(4) Before going home: wash hands carefully and rub in a little lanolin thoroughly.

At the same time, the employer must provide hot water, towels, and good quality hand soap. Moreover, it does no harm to demonstrate to the men how to remove grease from their hands by first rubbing in the soap with a minimum of water, and then swilling with water to remove the blackened soap solution. They then need a demonstration of how to apply the lanolin carefully, over and between the fingers and over the nail-beds, and if necessary up the forearms. 'Hand cleansers', with their fierce action on the skin, are not to be recommended.

THE WORKING ENVIRONMENT

The last few years have seen a shift of emphasis of interest from the clinical conditions which arise from environmental abnormality towards the measurement and control of the environment itself, and two societies have been formed to further this interest. The British Occupational Hygiene Society is composed of medical men, engineers and scientists, and it studies the physics and chemistry of the environment. The Ergonomics Research Society of medical men, anatomists, physiologists, psychologists and engineers, deals mainly with those aspects of the environment which lie within the field of human biology.

In parallel with these developments is a growing interest in the idea of the 'maximum allowable concentration' (Ministry of Labour, 1960b) in environmental control which sets upper safety limits for a large number of dusts, vapours, and other materials likely to be found in factories. It is, however, of little use being given a target if the distance from it cannot be measured, and to this end two occupational hygiene units have been established which are fully equipped to measure and advise upon aspects of the environment, such as dusts, vapours, temperature, airflow and noise. In the North the unit is located at Newcastle upon Tyne and in the South at Slough, Buckinghamshire.

INDUSTRIAL HEALTH SERVICES

During the last decade-and-a-half four industrial health services have been established through the generosity of the Nuffield Foundation or Trust. These services are different from each other and the next few years will prove an interesting period of study. The Slough organization is based on a trading estate and through full-time salaried staff provides a complete medical, traumatic and nursing service. An occupational hygiene team for environmental testing and advice has been associated with the Service for many years. In the new town of Harlow there is a family doctor service which links a number of practitioners in an original way with this expanding area of medicine. The North of England Industrial Health Advisory Service

is based upon the University Department in Newcastle upon Tyne, and it provides a complete occupational hygiene service supported by medical

	No. 1—Thursday, April 28	
2.30 p.m.	Introduction	By the Nuffield Professor of Industrial Health; Honorary Director, North of England Industrial Health Advisory Service
	The Family Doctor in Industrial Health	By the Director of the Harlow Industrial Health Service
4.0 p.m.	The Early Diagnosis of Industrial Disease	By the Reader in Industrial Health; Honorary Secretary, North of England Industrial Health Advisory Service
	No. 2—Thursday, May 5	
2.30 p.m.	The Work of the Occupational Hygiene Laboratory	By the Lecturer in Industrial Health (Occupational Hygiene)
4.0 p.m.	Visit to the Department of Industrial Health	
	No. 3—Thursday, May 12	
2.30 p.m.	Industrial Pulmonary Disease	By the Lecturer in Industrial Health (Pulmonary Physiology)
4.0 p.m.	Demonstration of cases in the Outpatient Department, Royal Victoria Infirmary	
	No. 4—Thursday, May 19	
2.30 p.m.	Industrial Accidents	By the Nuffield Professor of Industrial Health; Honorary Director, North of England Industrial Health Advisory Service
4.0 p.m.	The First-Aid Management of Hand Injuries	By the Reader in Experimental Surgery
	No. 5—Thursday, May 26	
2.30 p.m.	The Bad Back	By the Orthopædic Consultant Surgeon
4.0 p.m.	Accident Neurosis	By the Reader in Neurology
	No. 6—Thursday, June 2	
2.30 p.m.	Work and the Skin	By the Professor of Dermatology, and members of his staff
4.0 p.m.	Demonstration of cases in the Skin Department, Royal Victoria Infirmary	
	No. 7—Thursday, June 9	
	In the Ophthalmic Outpatient Department, Newcastle General Hospital	
2.30 p.m.	Work and the Eyes	By the Clinical Teacher in Ophthalmology; with the assistance of Senior Registrar
	No. 8—Thursday, June 16	
2.30 p.m.	Legal Aspects of Industrial Health	By H.M. Senior Medical Inspector of Factories to the Ministry of Labour
4.0 p.m.	Conclusion	

TABLE I.—Syllabus and timetable of a postgraduate course in Industrial Health held in the Medical School of King's College, University of Durham, during 1960.

advice upon industrial disease and long-term sickness. Another Service is being built up at Park Royal round the West Middlesex Hospital.

EDUCATION

There has been some progress in industrial health education since the war, and this advance at undergraduate level has been most marked in the provincial medical schools. Nearly all of these now combine field visits to places of work with more formal teaching by lecture or tutorial. One university also teaches industrial health to its engineers and its chemists, because they are the men who in future will be in charge of the environment in which other men and women work (Browne, 1954).

Postgraduate education today takes three forms: a course at three centres which leads to a Diploma in Industrial Health; courses at a number of universities which lead to the Diploma in Public Health, but which contain some industrial health; and part- or full-time refresher courses which may be designed on the lines of the syllabus of a course which was given to a mixed audience of family and industrial doctors (table 1). The absence of a postgraduate diploma has not turned out to be an impediment in gaining an appointment in the field of industrial medicine. Postgraduate courses, however, are becoming generally popular, and in this rapidly developing area of medicine it will become increasingly difficult to keep a practical grip on the subject without them.

References

Bouhuys, A., Lindell, S. E., and Lundin, G. (1960): *Brit. med. J.*, **i**, 324.

Browne, R. C. (1954): *Lancet*, **ii**, 400.

Cochrane, A. L., *et al.* (1961): *Brit. J. prev. soc. Med.*, **15**, 1.

Gilson, J. C. (1960): In 'Modern Trends in Occupational Health', ed. by R. S. F. Schilling, London, p. 50.

Grandjean, E. (1957): *Brit. J. industr. Med.*, **14**, 1.

Lane, R. E., and Dingwall-Fordyce, I. (1960): *Trans. Ass. industr. med. Offrs*, **10**, 26.

Leathart, G. L. (1960): *Brit. J. industr. Med.*, **17**, 213.

McCallum, R. I. (1960): 'Proceedings of the 13th International Congress on Occupational Health', New York, p. 741.

Miller, H. (1961): *Brit. med. J.*, **i**, 992.

Ministry of Labour (1960a): 'Annual Report of Chief Inspector of Factories on Industrial Health', 1959, London, H.M. Stationery Office.

—— (1960b): 'Toxic Substances in Factory Atmospheres', London, H.M. Stationery Office.

Newell, D. J., and Browne, R. C. (1955): *J. Fac. Radiol.*, **7**, 20.

Ramsay, J. H. Rolland, and Pines, A. (1959): *Brit. med. J.*, **ii**, 345.

Roach, S. A., and Schilling, R. S. F. (1960): *Brit. J. industr. Med.*, **17**, 1.

Shiels, D. O., *et al.* (1956): *A.M.A. Arch. industr. Hlth*, **13**, 489.

ADVANCES IN CLINICAL TOXICOLOGY

By C. J. POLSON, M.D., F.R.C.P.

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THE pattern of poisoning shows no material change since Fiddes (1955) gave details of the incidence of poisoning. Carbon monoxide continues to account for the majority of these fatalities and barbiturate poisoning is the commonest cause of non-fatal poisoning. There are occasional outbreaks of poisoning, as by tricresyl phosphate, but in the main, salicylates excepted, poisoning is otherwise sporadic. This must not obscure its clinical importance, since prompt recognition of the cause and the application of appropriate treatment will always be necessary. Poisoning by mercury or, more particularly, by lead has an uncanny knack of recurring in unlikely or unexpected situations. The preparation of home-made wine in glazed earthenware has provided a recent example (Whitehead and Prior, 1960). Despite the distinct success of measures to control mercurial poisoning in industry, it is still possible to encounter this and it continues to be a hazard in laboratories where liquid mercury is used in quantity, but where precautions are inadequate. The ancient craft of gilding is almost defunct, but Smith and Miller (1961) record chronic poisoning in one of the last of its practitioners. His predecessor had died of chronic mercurial poisoning and he had progressed to advanced tremor before it was recognized that his work was responsible for it.

PROTECTING THE CHILD

Accidental poisoning of small children continues to be a grave risk. Although these disasters are uncommon, they are increasing; they should not, and would not, occur if adults responsible for the care of children, especially those of from 1 to 2 years old, remembered the danger of leaving tablets in places to which children have access. These include mantelpieces, which a child can reach by climbing on a chair or table.

In a recent case, tablets of Easton's compound had been kept in a box in a vase on the dining-room table. A child, aged 19 months, climbed on to the table, ate some of the tablets and died of strychnine poisoning.

In another case, tablets of 'bidormal' were kept on a shelf in a hatch between the kitchen and the dining room. Although the evidence was equivocal, it is possible that the victim, a child aged 13 months, had reached the shelf and taken two or three of these tablets, one being enough to kill a child of that age.

When tablets which contain a Schedule IV drug are prescribed, the doctor should remember that the law does not require the container to be labelled

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'Poison' and therefore he should warn the patient that they are dangerous to children.

BARBITURATE POISONING

Although it may be that one standard treatment of poisoning by barbiturates has yet to be accepted, two methods now receive considerable support.

There are those who accept the Danish regimen, first described by Clemmesen (1954, 1959). This aims at maintaining the physiological condition during the patient's unconsciousness. Skilled nursing, parenteral fluid balance, continuous administration of oxygen and substantial doses of procaine penicillin are the essentials of this treatment. The patient is nursed in a slight Trendelenburg position and there is a two-hourly change of posture. The air passages are aspirated and, if there is appreciable obstruction, intubation is done. Respiratory paralysis is relieved by artificial respiration. Blood transfusion or glucose infusion is also practised. It was claimed that this regimen reduced the mortality from 24.8 per cent. to only 1.6 per cent.

The alternative method, which has considerable support in this country, is based primarily on the administration of bemegride. This is an analeptic, the action of which is of longer duration than leptazol, nikethamide or picrotoxin. The effects of one injection last from 10 to 20 minutes. It is used in conjunction with amiphenazole, a respiratory stimulant of special value in severe poisoning by the long-acting barbiturates. Bemegride is normally sufficient of itself for the treatment of poisoning by short-acting barbiturates. It has an additional value, in that it reduces the risk of bronchopneumonia. Shulman and his colleagues (1955) claimed success in 40 of 41 patients treated with bemegride.

These drugs are administered by injection into the tubing of a glucose infusion apparatus, used to administer 5 per cent. glucose infusion. When that infusion has been arranged, and both drugs are used, 1 ml. of 1.5 per cent. amiphenazole (15 mg.) is first injected into the tubing and this is followed by the injection of 10 ml. of 0.5 per cent. bemegride (50 mg.). These injections are repeated every three to five minutes, as required. When the patient is in deep coma the treatment may have to be continued for upwards of two hours, during which time 20 ml. (or 300 mg.) of amiphenazole and 200 ml. (or 1 g.) of bemegride may have been administered.

The prognosis of barbiturate poisoning is improved, if the rate of excretion of barbiturate is increased. Lassen (1960) has therefore proposed forced diuresis and alkalinization of the urine as an adjunct to the Clemmesen regimen. He recommends the administration of urea as a diuretic and sodium lactate as an alkalinizing agent. The effect of the latter can be augmented by subcutaneous administration of sodium bicarbonate. The dialyser is the patient's own kidneys, which are effective to the equivalent of using the artificial kidney for about eight hours a day. It is yet too early to assess whether this method yields better results than hæmodialysis. Lassen points out that the latter procedure is difficult to maintain continuously in a patient who is critically ill and in the face of circulatory instability.

Lassen's series of 14 patients had been unconscious for from 7 to 115

hours and had taken from 5 to 18 g. of barbiturate. Thirteen survived and the fourteenth died of pulmonary embolism. Diuresis occurred up to 11 litres of urine in twenty-four hours. Although the amount of drug excreted differed according to the barbiturate taken, it was increased in all cases. The period of unconsciousness was reduced: i.e. down to one-third of the usual period, with diethyl, diethyl + isopropyl and ethylallyl barbituric acid. The treatment was least effective with diallyl barbituric acid. That is to say, it is of greater value with long- and medium-acting than with short-acting barbiturates. Lassen also believed that even when all of the drug taken had not been absorbed from the stomach, this treatment would reduce the level of anæsthesia and the period of unconsciousness. It is believed that the treatment had been life-saving in at least three of the patients. It requires a good deal of control by laboratory investigation and constant nursing attention for a period, on the average, of about forty-two hours. There was transient pulmonary œdema in one patient and severe dehydration in another.

LEAD POISONING

Outbreaks and sporadic cases of poisoning by lead continue to occur. The sources have ranged from nipple shields to newsprint, used as toilet paper. Home-made wine is a recent addition to the list. Elderberry wine 'of a rich, red colour and . . . a not unpleasing bouquet' was the vehicle and the source was lead glaze on the interior of a jowl used in wine-making. The vessel had been inherited from an aunt and had 'a local reputation for the flavour of the wine produced in it'. The patient was treated successfully with edathamil calcium-disodium (E.D.T.A.) (Whitehead and Prior, 1960). Lead poisoning due to the use of lead-glazed pottery in which to boil wine or store pickled cucumber occurs in Jugoslavia. It appears that lead poisoning from lead-glazed pottery is also common in Russia (Beritić and Stahuljak, 1961). This lesson seems hard to learn, because the danger of lead-glazed vessels was recognized as early as 1754, when Lind reported serious contamination of fresh lemon juice prepared in a glazed coarse earthen vessel.

The significance of pica as a clue to poisoning by lead is stressed by Shrand (1961). It takes about three months for an infant to nibble enough of the paint to produce symptoms of lead poisoning. Yet the diagnosis and treatment must be prompt. The occurrence of pica therefore demands the exclusion of lead poisoning as the first step. Estimations of the lead content of the blood or urine are the usual investigations, but Shrand points out that these take time. He indicates several screening aids which yield a presumptive diagnosis: pica is outstanding in that the probability of a positive result is 90 to 100 per cent. Blood examination may show basophilic stippling in 18 per cent. and x-ray examination of the abdomen or long bones in 30 per cent. Coproporphyrinuria or urinary-amino-lævulic acid each have a probable positive value of 100 per cent.

Treatment.—Acute poisoning following the ingestion of a soluble salt of

lead requires prompt gastric lavage with a 10 per cent. solution of sodium or magnesium sulphate. E.D.T.A. also has value.

Chronic poisoning is treated by chelating agents and that now generally accepted as efficient is E.D.T.A., the calcium chelate of disodium ethylenediamine tetra acetic acid (edathamil calcium-disodium). The calcium in the drug is readily displaced to form a non-toxic, non-ionized, but soluble, lead compound, which is readily excreted in the urine. The drug may be administered by slow intravenous infusion; it is dissolved in normal saline or glucose saline in a dosage of 350 to 700 mg. per kg. of body weight per day. The usual course lasts four to five days and may be repeated, after an interval of two days. There follows a massive increase in the urinary excretion of lead, of up to 10 mg. in twenty-four hours. Symptomatic treatment is also necessary. Abdominal colic, for example, is relieved by warmth or firm pressure on the abdomen, or, better, by atropine 1/100 grain (0.6 mg.) subcutaneously, or glyceryl trinitrate 1/130 grain (0.5 mg.) sublingually. The restlessness of lead encephalopathy may require barbiturates or paraldehyde.

Infusion treatment demands admission to hospital and, as Shrand (1961) points out, intravenous infusion is a formidable procedure for children and not without danger, if the brain is already œdematous. He rejects subcutaneous infusion for like reasons. Oral administration is of value only in mild cases. Shrand has found that intramuscular injections of E.D.T.A., 0.5 per cent. combined with procaine, 0.5 per cent., and chlorocresol, 0.5 per cent., caused no local reactions or pain when injected into the buttock. Excretion of lead was satisfactory and there was rapid clinical improvement. Severe poisoning in a boy, aged 2, was relieved by a course of injections, totalling 75 mg. per kg. during every 24 hours, for five days. It is possible to use this method for treatment at home, but when there is encephalopathy, admission to hospital must be immediate.

E.D.T.A. has also been used in the treatment of plutonium poisoning (Foreman *et al.*, 1956).

NARCOTIC POISONING

Nalorphine is now established as the best antagonist of narcotics. The drug is relatively non-toxic. It causes mild drowsiness, irritability, miosis, pallor and sweating; it may cause nausea and hot and cold flushes. The drug reduces, if it does not abolish, most of the characteristic actions of morphine, other opiates and drugs of like pharmacological action: i.e. pethidine, methadone and alphaprodine. A dramatic stimulation of respiratory rate and volume will occur within seconds after an injection of the drug. It reverses the fall in blood pressure and decrease in pulse pressure. The victim awakens from the narcotic state.

Nalorphine is invaluable in the treatment of acute narcotic poisoning, as by accidental overdosage. Unfortunately, it is of no value in the treatment of addiction to narcotics, since its use induces a typical withdrawal syndrome. This effect has value in establishing the diagnosis of addiction in a doubtful

case. The drug is useless in the treatment of poisoning by barbiturates, cyclopropane or ether. The dosage of this drug is from 5 to 10 mg. (1/12 to 1/6 grain), administered intravenously (Nalorphine Injection B.P. contains nalorphine hydrobromide 10 mg./ml., unless otherwise directed). It is our experience that if this drug is to be effective, the initial dose should be one of at least 10 mg. The dose may have to be repeated at intervals of not less than fifteen minutes and a total dosage of up to 40 mg. may be required in a case of severe poisoning. It can also be administered intramuscularly or subcutaneously. This specific treatment must be accompanied by the usual supportive measures.

Nalorphine has a place in midwifery in the relief of neonatal asphyxia, since the drug has been shown to pass the placental barrier. About ten minutes before the time of delivery the mother receives 10 mg. intravenously; alternatively, 0.25 to 1 mg. can be injected directly into the umbilical vein of the new-born infant.

POISONING BY ORGANIC DERIVATIVES OF PHOSPHORIC ACID

Although organic derivatives of phosphoric acid were first prepared for use as war gases, it was later discovered that they were substitutes for nicotine as pesticides and today 'parathion', 'metasystox' and 'malathion' are widely used in agriculture; some are also available for domestic horticulture. The toxicity of these substances depends on the presence of the P:O group in their molecule, the effect of which is to inhibit cholinesterase and, in consequence, there is then an accumulation of acetylcholine. Tetraethylpyrophosphate (T.E.P.P.) and 'parathion' are highly toxic, whereas 'malathion' is almost innocuous. The lethal dose of T.E.P.P. is 2 and that of 'parathion' 4 to 13, whereas that of 'malathion' is only 1000 to 1300 LD_{50} (mg./kg. for rats) (Gage, 1961). The lethal dose of 'parathion' for man was estimated at 12 to 20 g. (Kanagaratnam *et al.*, 1960).

Up to the present 'metasystox' (LD_{50} 80) and 'malathion' are alone used extensively in this country. Gage (1961) could recall only one fatality due to contact with organic phosphoric pesticides, a 'parathion' death in 1952 or 1953. The low toxicity of 'malathion' is indicated by his case of a woman who applied it to an aching tooth and inadvertently swallowed the contents of a 16-ounce (570 ml.) bottle. Except for vomiting, she suffered no ill effects. In other countries, where 'parathion' is extensively used, and where precautions are inadequate, as in Japan and Egypt, accidental, fatal poisoning is still common. Elsewhere, notwithstanding extensive use of 'parathion', but where safety precautions are observed, accidental poisoning is uncommon. It has been found, however, that in those countries, 'parathion' has become a common agent of suicide. Toivonen and his colleagues (1959) reported that in Finland during 1952-57 suicidal poisoning accounted for 237 of the 286 deaths due to 'parathion' poisoning. The suicide incidence had risen from one case in 1952 to 94 'parathion' suicides in 1957. In Copenhagen, 'parathion' poisoning accounted for 73 of 2,044 consecutive

cases of fatal poisoning during 1953-1959 and took third place after poisoning by carbon monoxide, 1,286 cases, and barbiturates, 540 cases. All of the 'parathion' deaths in this series were by suicide; the absence of accidental poisoning was ascribed to adequate precautions (Gormsen, 1961).

Accidental poisoning with these substances is normally a result of contact during their use in agricultural operations. There is a possibility of poisoning from the ingestion of contaminated food. This is as yet rare, but it can arise when food is stored in the vicinity of a spraying operation. An outbreak of 'parathion' poisoning in Singapore was due to contact with poisoned barley. Some drank barley water prepared from the grain and others ate the grain. The severity of symptoms, as might be expected, was least in those who drank the barley water, and was proportional to the amount of grain eaten. Thirty-five children and three adults were affected and nine of the children died. Atropine was then the only drug available for treatment (Kanagaratnam *et al.*, 1960).

'Parathion' is a rapid poison, since death following a lethal dose normally occurs within one-half to four hours. Kaye (1954) has cited a death within two minutes. After absorption, the bulk of the poison is stored in skeletal muscle; a small amount is present in the blood, brain, liver, kidney and lungs.

An analysis showed that the proportion in a body after death was as follows: stomach and contents, 4000 mg.; skeletal muscle, 165 mg.; blood, 8 mg.; liver and other organs, 2 to 4 mg. (Pribilla, 1955).

Cholinesterase is a relatively stable enzyme and remains active in the blood and brain for several days, if the samples are taken within thirty-six hours after death and are stored in a refrigerator. Such samples have value in the detection of 'parathion' poisoning, except when the death is rapid, following the ingestion of a large dose. In the latter circumstances, the determination of cholinesterase must be prompt, since enzyme regeneration can occur in stored material from such victims (Gage, 1961).

Prevention of poisoning by 'parathion' is possible, and effective safeguards, if rigorously observed, give well-nigh complete protection. Only those trained in the use of this pesticide should be permitted to use it. They must be protected by suitable clothing and, when engaged in spraying, they should wear masks. The clothing must be changed daily and washed before it is used again. If a worker is splashed with the solution, he must change his clothing at once. Those who handle the soiled clothing must be trained to exercise care. Smoking or eating is prohibited until the worker has washed his hands. It is also necessary that all workers in contact with 'parathion' are aware of the symptoms of poisoning, so that they are prompt to seek treatment if affected. Control of the health of the workers is also exercised by weekly observations of their plasma cholinesterase activity. This should not fall below 60 per cent. of the normal level. It is even more important to take note of the rate of fall, which has greater significance than the actual level.

The safety of workers with organic phosphoric pesticides is also further safeguarded by the recent agreement which has been reached between the Ministry of Agriculture, Fisheries and Food and the producers and distributors of these and kindred products. The Government will be advised of any proposal to introduce new chemicals into agricultural practice. The toxicity of the substance and all relevant information will be disclosed, so that the Government can advise on the precautions to be taken to protect workers, consumers, domestic animals and wild life. The information will relate not only to products which contain a completely new principle, but also to new formulæ of active principles already known and to any extension of use of any existing product, when that is likely to create new or unusual risks. This voluntary agreement has been deemed preferable to statutory regulations (Ministry of Agriculture, Fisheries and Food, 1960).

Treatment.—The original curative treatment of 'parathion' poisoning was continuous administration of atropine. It still has a place, but it can counter only the muscarine effects of the poison; atropine does not prevent muscle fasciculation, due to nicotinic acid. Cholinesterase is reactivated by pyridinealdoxime methiodide; this drug and P_2S, the corresponding methane sulphonate, are the specific antidotes. Pyridinealdoxime methiodide is administered intravenously in doses of 1 to 2 g. and this is followed by a rapid subsidence of symptoms. There is an immediate rise in the red-cell cholinesterase, but from two to three weeks elapse before the serum level returns to normal. Another drug which has recently been investigated, but which has so far not been used in man, is monoisonitrosoacetone, which is apparently a more powerful reactivating oxime than pyridinealdoxime methiodide: roughly about 10 times greater (Hobbiger, 1961).

TRICRESYL PHOSPHATE (T.O.C.P.) POISONING

This organic compound of phosphorus is primarily an insidious neurotoxin; it may or may not inhibit cholinesterase. Poisoning by T.O.C.P. in this country is as yet rare, but an outbreak occurred on Merseyside in 1945. Serious outbreaks have occurred elsewhere and there appears to be a continuing risk. Bootleg whisky contaminated with T.O.C.P. was responsible in 1930 for an outbreak in the United States, where the resulting illness became known as Jamaica ginger paralysis, since sugar and ginger then used were adulterated with T.O.C.P. In other countries the outbreaks have been due to adulteration of cooking oil with T.O.C.P.: e.g. an outbreak in Switzerland and another in South Africa, involving also persons who sailed in the *Jean D.* from Durban. The most recent outbreak, estimated to have involved 10,000 people, occurred in Morocco in 1959. It appears that surplus aircraft oil, used to rinse turbo-jet engines at an American base in Morocco, was bought by unscrupulous persons. They mixed it, as to 20 per cent., with peanut 'olive' oil and sold the mixture as cut-price cooking oil. Some brands of hair oil were also believed to contain this aviation oil. About 6000 persons, of whom about 50 per cent. were under 18, became paralysed, and

some were completely paralysed. The British Red Cross sent a party of physiotherapists to rehabilitate the victims. Later, 24 Moroccan merchants were sent for trial and the late King Mohammed V gave instructions that those found guilty of knowingly selling this substance as 'pure vegetable oil' should be sentenced to death.

The outbreak on Merseyside in 1945 involved 17 people. At first, their illness was believed to be simple gastritis, or influenza, but when the ninth victim was seen, the possibility of T.O.C.P. poisoning was recognized. Inquiries then showed that the patient had been given some cotton-seed oil, which he had shared with others. It was used to fry potatoes. Examination of the oil showed that it was contaminated by T.O.C.P., derived, in all probability, from the use of second-hand containers (Hotston, 1946).

Sporadic cases of poisoning by T.O.C.P. have resulted from the use of apiol, adulterated with T.O.C.P., as an abortifacient. The case described by Hermann and his colleagues (1956) appears to be unique in this country.

The illness begins with a gastro-intestinal upset, which resolves within a few days. Several days—ten to fifteen—elapse before neurological damage is apparent. The patient then has signs of flaccid paralysis of the legs, with foot-drop and, sometimes, pain in the calves. Paralysis, with wrist-drop, may extend to involve the arms, but this is less severe than in the legs. Cerebral involvement is rare. At the outset the diagnosis is difficult, but any outbreak of polyneuritis or atypical poliomyelitis should bring to mind the possibility of poisoning by T.O.C.P.

Unfortunately, there is no specific treatment. Recovery is slow, but may be hastened by appropriate physiotherapy. Most of the victims recover, but the illness may last over two years.

References

Beritić, T., and Stahuljak, D. (1961): *Lancet*, **i**, 669.
Clemmesen, C. (1954): *Acta med. scand.*, **148**, 83.
—— (1959): *Dan. med. Bull.*, **6**, 209.
Fiddes, F. S. (1955): *The Practitioner*, **175**, 479.
Foreman, H., *et al.* (1956): *J. Amer. med. Ass.*, **160**, 1042.
Gage, J. C. (1961): *Med. Sci. Law*, **1**, 137.
Gormsen, H. (1961): *Ibid.*, **1**, 160.
Hermann, K., Le Roux, A., and Fiddes, F. S. (1956): *Lancet*, **i**, 937.
Hobbiger, F. (1961): *Proc. roy. Soc. Med.*, **54**, 403.
Hotston, R. D. (1946): *Lancet*, **i**, 207.
Kanagaratnam, K., Boon, W. H., and Hoh, T. K. (1960): *Ibid.*, **i**, 538.
Kaye, S. (1954): 'Handbook of Emergency Toxicology', Springfield, Ill., quoted by Toivonen *et al.* (1959).
Lassen, N. A. (1960): *Lancet*, **ii**, 338.
Lind, J. (1754): *Scots Magazine*, **16**, 227; quoted by Meiklejohn (1954).
Meiklejohn, A. (1954): *Brit. J. industr. Med.*, **11**, 40.
Ministry of Agriculture, Fisheries and Food (1960): 'Notification of Pesticides'. Memorandum No. 69158.
Pribilla, O. (1955): *Arch. Toxikol.*, **15**, 210.
Shrand, H. (1961): *Lancet*, **i**, 310.
Shulman, A., *et al.* (1955): *Brit. med. J.*, **i**, 1238.
Smith, A. D. M., and Miller, J. W. (1961): *Lancet*, **i**, 640.
Toivonen, T., Ohela, K., and Kaipainen, W. J. (1959): *Ibid.*, **ii**, 175.
Whitehead, T. P., and Prior, A. P. (1960): *Ibid.*, **ii**, 1343.

ADVANCES IN GENERAL PRACTICE

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THE practice of medicine has in recent years undergone such rapid change that there is uncertainty and in some quarters at least even a little disquiet as to the probable role of the family doctor in the immediate future. For example, such is the uneasiness about differences between hospital medicine and family medicine and their implications for the training of medical students that our old friend the Y plan has recently been resuscitated, reconsidered and debated (Rutstein, 1961; *Proc. Roy. Soc. Med.*, 1961). Perhaps the most significant sign of the times, however, and in this context the most important single event in recent years, was the publication of Dr. Fox's essay on the personal doctor (1960). Fox's particular contribution to general practice lies in his challenge to us to ask ourselves where do we go from here and how do we define what constitutes an advance?

A DEFINITION

If I had been preparing this article a mere decade ago I would not have thought it necessary either to begin with a definition of general practice or to question the assumption that the general practitioner was an essential, continuing and integral part of our services for the provision of medical care for the community. In this discussion of some events which might be considered in a review of advances in general practice, it is perhaps desirable, however, to set down a simple definition. There are in my opinion two characteristics which distinguish the general practitioner from his colleagues in other fields of medicine. The first is that he practises in a field which is of necessity undifferentiated. He cannot, and may not, predetermine the kind of clinical or social challenge with which his patient may confront him. He may not allow his skills and interests to become so differentiated and limited that they qualify the degree of freedom of access to him which his patients must enjoy. Secondly, he must accept responsibility for the continuity of provision of personal care for his patients. In this context one might assess the claims that a particular event be judged as an advance in general practice by posing these questions. Has it resulted in an improvement in the diagnostic and therapeutic skills and services which the general practitioner offers to his patients? Does it enhance the quality of the continuing personal care which he provides?

The quality of general practice at a given point in time depends on three factors: (a) existing medical knowledge; (b) the circumstances in which the family doctor practises—the diagnostic and therapeutic tools at his disposal, the amount of time that he can give to his patients, the organization of hospital and community services, both medical and social, and the

administrative arrangements prevailing at that point in time; and (c) the personal attributes of the doctor himself, his technical skills, and his knowledge and insight—factors which are to some extent controlled by our methods of selection of medical students, the way we train them, and the doctor's postgraduate training and experience. These three factors, of course, interact on each other in varying degree but, if the personal qualities of the general practitioner are reasonably adequate, his basic training sound, and his continuing education assured, and if the circumstances in which he practises are adequate, i.e. if we can provide him with adequate time, tools and training, then any advances in medical knowledge, skills or techniques will automatically result in an advance in the quality of service provided by the family doctor.

APPLYING KNOWLEDGE

I do not propose to make an appraisal of the many technical and scientific advances which in recent years have been ploughed back into general practice with a consequent improvement in the diagnostic and therapeutic services which the family doctor can now provide for his patient, although I am not unmindful of such innovations as the introduction of a wider and more effective range of oral diuretic and anti-diabetic agents, the use of new drugs in the management and control of gross psychiatric disorders, and the introduction of simple manageable diagnostic techniques such as the enzyme reagents covering a wide range of biochemical aids to diagnosis, and the use of the Ayre spatula and cytological screening in the early diagnosis of cancer of the cervix uteri. My fellow-contributors to this Special Number will provide evidence of substantial advances in at least seventeen subjects whose academic content and clinical interests are fairly well defined. Many such advances will in due course become incorporated into general medical practice so that it is a truism to say that much of what is hospital or specialist practice today will become general practice tomorrow. It is not every advance in knowledge that has an obvious relevance for the family doctor, nor do all such advances come from the medical sciences alone, but major advances in general practice must inevitably be preceded by the advancement of knowledge. Too often, however, advance is halted by our failure to apply existing knowledge. It would appear that as in many other spheres so also in medicine are we more skilful in advancing knowledge than in applying it. I suggest therefore that a search for evidence that a true advance in general practice has taken place or is likely to take place might most profitably be concentrated on the second and third groups of factors which determine the quality of care provided by the general practitioner.

EDUCATIONAL AND ACADEMIC ASPECTS OF GENERAL PRACTICE

In a recently published article in which he reviews the limitations of medical care attributable to medical education, McKeown (1961) suggests that at present we are attempting to prepare students for the practice of

medicine by methods more appropriate to its advance. The tendency in medical schools to the artificial separation of teaching and research from the actual practice of medicine is one of the by-products of specialization. This atmosphere in which the student acquires his basic intellectual skills and equipment is particularly unfortunate so far as the future family doctor is concerned who, when he leaves his medical school, finds himself in a situation where the picture is completely reversed and the daily practice of medicine consumes all his energy. The general atmosphere is not particularly conducive to academic learning and the pursuit of new knowledge, and he is suddenly alone and deprived of the daily stimulation and conversation of colleagues and teachers whose interests lie mainly in the academic field. The general practitioner, possibly more than any of his colleagues, is unusually exposed to the hazards of professional isolation. Isolation from fellow-practitioners, from colleagues in the preventive and social fields, from hospital colleagues, and from academic teaching and research institutions, was the common experience of the majority of general practitioners until comparatively recently. Before the introduction of the National Health Service the majority of general practitioners were in single-handed practice; now an ever-increasing majority work in partnership. The Danckwerts Award with the introduction of the idea of the notional list has done a great deal to accelerate this trend. Whatever the disadvantages of partnership practice to the patient or the doctor, there can be little doubt that partnership, group or health centre practice, tends to break down professional isolationism, to promote academic and clinical exchange, and to facilitate arrangements whereby the general practitioner can take advantage of existing opportunities for continuing postgraduate training.

The establishment of a College of General Practitioners in 1952 probably did more than any other single thing to provide an antidote to professional isolationism and a vehicle by which general practitioners could meet and exchange views, information and skills, and develop the means of promoting their own academic advancement. I suggest therefore that this breaking down of professional isolation must be welcomed as an advance in general practice in so far as it has prepared the way for the acceptance of general practice as an academic entity. This is a necessary first step towards serious study of the professional, scientific and academic problems confronting the general practitioner. Evidence that an increasing number of individuals see the need for such basic ground work and study as a preliminary to further advance must be among the most encouraging omens for the future of family medicine. Academic developments in general practice are conveniently discussed under the headings of undergraduate education, postgraduate education and research.

UNDERGRADUATE EDUCATION

The past decade has brought a more general acceptance on the part of medical schools of the need to introduce the student to general practice

during his undergraduate years. Almost every school in this country now makes some provision, usually on a voluntary basis, for students to see something at first-hand of the work of the family doctor. The arrangements vary greatly and there is still no obvious common pattern of intention or purpose in promoting these excursions into general practice. In these circumstances it is difficult to forecast the effect that they will have on the next generation of medical graduates. Some advocates of this kind of teaching experience (including in some instances students themselves) are inclined to stress the vocational aspect and to see in these ventures a means of raising the standard of general practice by implementing a recommendation of the Goodenough Committee to the effect that medical schools in designing their curricula and in deciding on emphasis should always have at the front of their minds the needs of future family doctors. With recent changes in emphasis in the recommendations made by the General Medical Council and encouragement given to medical schools to experiment with their curricula, it might be argued that some schools could with advantage develop this aspect of training with the clear intention of producing more adequately equipped embryo family doctors.

All the evidence, however, suggests that medical schools are moving farther away from vocational trends in training, and are emphasizing the fact that it is their job to provide training which is truly basic to all branches of medicine (including general practice). This is an encouraging sign at a time when the proposition of dual curricula has been raised elsewhere, although it is paradoxical that at a time when general practice is more sharply differentiated from hospital practice than ever before we should accept less responsibility in our medical schools for concerning ourselves with the professional future of our graduates who are destined for general practice. On the other hand, if more students are gaining practical experience and instruction in the milieu of general practice, and if those who are responsible for providing this instruction and supervising its content and emphasis are determined to avoid the temptations of vocational training, then we must surely produce a better generation of doctors, in whatever branch of medicine they practise, who have greater understanding of the need for collaboration and integration with their colleagues in other fields, and of the need to equip themselves by training, study and research, to resolve the major problems with which society confronts our profession in our attempts to provide scientific, comprehensive, integrated, personal medical care.

Among the promising recent events in the field of undergraduate education has been the creation of a British Association for the Study of Medical Education. Established on a broad basis, recruiting its membership from all medical schools, our medical colleges and licensing bodies, it has devoted most of its energy so far to promoting research inquiry and investigation into the needs of the undergraduate. Whilst in its early years it has tended to confine itself to such questions as the selection of students, the examina-

tion system, and the design and function of teaching hospitals, it has shown itself willing and able to tackle more ambitious and long-term projects such as the study of how students learn and how their attitude to medicine and to the profession evolves. The Association also plans to examine the place of general practice teaching in the undergraduate curriculum. This preoccupation with the need to review undergraduate teaching in the light of new developments in the practice of medicine outside the hospital is not confined to this country, and it is relevant to note that a European conference under the auspices of the World Health Organization met last month to examine 'the education and training of the doctor for his work in the community'.

Those of us who have practised family medicine with a student at our elbow have no doubt that whatever the student may gain, the patient certainly benefits from having a doctor who is being kept up to date, on his toes, more thorough and alert, and less complacent and opinionated as the result of this exposure to a critical if junior colleague. It is not our primary object, however, to teach students what general practice is in 1961, but rather to equip them to be able to face the challenge of general practice in 1981. Current changes and shift of emphasis in undergraduate teaching will not therefore result in any major advance in general practice for some time to come. The harvest from these changes, which are welcome but are comparatively recent, is still to be reaped. It is to postgraduate teaching that we have to look for more immediate evidence of academic activity contributing to advances in general practice.

POSTGRADUATE EDUCATION

For the past decade all new recruits to general practice have had at least one year's hospital experience after medical qualification, and many continue far beyond this minimum period of hospital training. A recent report (Report of Joint Working Party, 1961) recommends at least two years' hospital preparation for general practice, and this trend is to be welcomed in view of the North Carolina findings that clinical competence in general practice correlates closely with the length of time spent by the doctor in his postgraduate hospital preparation for family medicine.

For the doctor already established in general practice the range and scope of postgraduate educational facilities have increased quite strikingly in the past few years, and a substantial number of general practitioners who had little if any postgraduate training are now freely availing themselves of these facilities. The College of General Practitioners has given a lead here with its insistence that its members be required to continue their postgraduate training so long as they remain in general practice. The College, too, has supplemented the statutory sources of postgraduate training by creating additional facilities: e.g. by arranging colloquia, symposia and week-end conferences. Two College activities are particularly worthy of comment, namely, their recording service and the Upjohn Fellowships. The

former provides a circulating library of specially prepared tape recordings and gramophone records, sometimes supplemented by written material and visual aids which are of particular value to the isolated practitioner. The latter enables some 15 to 20 general practitioners each year to spend periods of up to four weeks or occasionally longer, visiting hospitals, laboratories, fellow practitioners, health centres and similar institutions, in pursuit of an individual programme of postgraduate training or in preparation for a specific study which cannot be supported by any existing arrangements.

A similar but more ambitious programme was introduced last year by the Nuffield Foundation. In each year of this five-year programme three general practitioners from the United Kingdom will spend six months abroad studying some facet of general practice in another country, and bringing back ideas and lessons to be ploughed back into general practice in Great Britain. An additional two Fellowships enable a general practitioner from Australia and one from Canada to pay similar visits to this country. This is but one example of a trend towards international academic exchange in the field of general practice which is to be welcomed.

Most postgraduate training programmes for general practitioners tend to follow traditional and well-tried paths with regard to both subject-matter and method. As an example of the less orthodox, mention should therefore be made, in this context, of the contribution of Michael Balint and his colleagues (Balint, 1957) to the in-service postgraduate training of the general practitioner. Whilst we have as yet no yardsticks by which to measure the impact of these and similar experiments in training, their focus on the dynamics of the doctor-patient relationship must surely be welcomed by those who advocate an improvement in the quality of the personal care provided for his patients by the family doctor.

THE TRAINEE ASSISTANT SCHEME

The trainee assistant scheme must surely receive a mention among the advances which have taken place in general practice, particularly since the inception of the National Health Service. Many of the criticisms of this scheme have been used as a basis for its improvement. The College of General Practitioners has studied this subject, and a booklet for the guidance of trainers has now achieved a second edition. In pre-Health Service days the Department of Health for Scotland introduced a two-year programme which combined hospital and general practice training to meet the special needs of practitioners who were to be working in the remoter highlands and islands. It is interesting to note that this idea has been resuscitated and regional committees have been encouraged to develop schemes which will extend the traineeship and incorporate hospital as well as general practice experience. An experimental scheme along these lines has been established at Winchester with the support of the Nuffield Provincial Hospitals Trust. If the Platt Committee's recommendations are implemented, particularly those recommending that all future general practitioners should have at least two

years' hospital experience and that suitably trained general practitioners should be encouraged to work part-time in hospital either as clinical assistants or as a new-type medical assistant, then we can anticipate a wider, more general, implementation of these experiments with the trainee assistant scheme.

RESEARCH IN GENERAL PRACTICE

Family medicine is no different from hospital medicine in at least one respect: namely, that advances are most likely to take place and standards to be raised where there is close association and exchange between practice, teaching and research. In this context research should not be judged only on the basis of the results of inquiry, survey or experiment, important as these contributions are to new knowledge and new techniques. Organized curiosity can be a highly contagious condition. Contact and exchange between family doctors sharing an enthusiasm for inquiry, and between general practitioners and those working in other fields, must surely be noted in any review of actual or potential advances in general practice. There are encouraging signs here, of which the following may be noted as examples.

A working party of the committee for social and environmental medicine of the Medical Research Council was set up as long ago as 1953 to study ways in which the Council might promote research in the field of general practice. Two years ago the Medical Research Council decided that progress had been sufficient to justify changing the status of the working party to that of a permanent committee (M.R.C. Report, 1959). The committee has itself initiated research projects, such as their inquiry into the natural history of acute otitis media in general practice, and a study of the way in which staphylococcal infections are introduced into families, but perhaps their chief contribution has been that of reviewing the practical and technical problems confronting general practitioners and others wishing to pursue research in the setting of general practice. In this connexion the committee has had profitable exchanges with the research organization of the College of General Practitioners. Since its inception in 1952 this College has made a considerable impact by stimulating interest in this field on the part of its members and in particular by harnessing the enthusiasm and energy of some 700 volunteers who in various ways and in different degrees have been helped to participate in joint collaborative studies. It is perhaps too early to expect fundamental or dramatic advances in this field, but the possibility of canalizing the enthusiasm and energy of such a substantial number of the members of this College is one of the pointers to a brighter future. The College certainly takes this facet of its work seriously and has already earmarked for the establishment of a College research foundation £100,000 out of the sum so far collected in its general appeal.

The older foundations have certainly not been backward in their support of growing points in teaching and research in the general practice field. It was through the generosity of the Rockefeller Foundation that a teaching and research unit in general practice was set up under the ægis of the

University of Edinburgh, and this same Foundation in collaboration with the Nuffield Foundation supported the setting up of the University health centre in Manchester. A review of the grants made recently by the Nuffield Provincial Hospitals Trust (1961) shows evidence of activity in this field and the promise of more to come. As examples can be quoted their support of experimental diagnostic centres for general practitioners in Corby and Edinburgh, their support of a statistical advisory service for general practice in association with the College of General Practitioners, the current study of relationships between hospitals, general practitioners and patients which is being carried out at the Institute of Community Studies, and the studies of the social case-work component of general practice being carried out at Rugeley and at Cardiff.

ORGANIZATION AND ADMINISTRATION

In recent years certain aspects of the structure and function of our general practitioner services have been studied by individuals, groups, committees and commissions: e.g. our maternity services have been reviewed (Report of Maternity Services Committee, 1959), the social aspects of prescribing have been subjected to detailed statistical analysis (Martin, 1957), and two committees on prescribing (Report of Committee on Prescribing Costs, 1959; Report of Scottish Committee on Prescribing Costs, 1959) have made recommendations, some of which have already been implemented. General practitioners now enjoy a greater freedom of access to the laboratory and other diagnostic facilities of the hospital and specialist services than was the case five years ago. Nevertheless, it would be unrealistic to suggest that there have been any recent major administrative changes which are calculated to lead to substantial advances in general practice. On the contrary it is disappointing to record that the Royal Commission on Doctors' and Dentists' Remuneration (1960) did not see fit to make any recommendations regarding the maximum number of patients on a doctor's list. Time, tools and training are among the most urgent of the general practitioner's needs and, although there is substantial opinion that giving the family doctor more time to examine and listen to his patients would certainly enhance the quality of the service, the past five years have not brought any substantial reduction in the average number of patients on the doctor's list. It is not always easy to differentiate between the administrative and academic components of the problem of improving our general practitioner services. The two facets are obviously interdependent, and action in both fields is clearly a prerequisite to major improvements in the quality of general practice.

QUALITY OF MEDICAL CARE

Nearly five years have elapsed since Peterson and his co-workers (1956) first published the results of an analytical study of general practice in North Carolina. Whatever the view taken about the validity of the findings, the interpretation of their significance, and their applicability to general practice

in this country, the study itself is of special significance as an example of an attempt to measure and record objective data as a step towards evaluation of quality in general practice. There are some signs that during the past five years some workers in this country are beginning to take up the challenge. For example, in the report of their study of the demand for m dical care, Forsyth and Logan (1960) draw certain conclusions about the quality of general practice from their experience of examining the use of local hospital outpatient departments. Other current studies, including some already referred to, also show a preoccupation with the evaluation of quality in medical care. These are all hopeful signs, but the basic question still remains—how to define quality of medical care in general practice, and to differentiate between good and bad or better and best. In this context perhaps the most significant recommendation of the Royal Commission was that £1,000,000 be set aside annually as an award for quality. If, as I believe, this recommendation has revealed that there does not yet exist a satisfactory objective yardstick for measuring quality of service given by the family doctor and if this state of affairs in turn leads on to a series of well-planned operational studies of the nature of general practice itself, then our successors may well point to this as the most significant event in this era, in bringing about a fundamental advance in general practice.

References

Balint, M. (1957): 'The Doctor, His Patient and the Illness', London.

Forsyth, G., and Logan, R. L. F. (1960): 'The Demand for Medical Care', London.

Fox, T. F. (1960): *Lancet*, **i**, 743.

McKeown, T. (1961): *Ibid.*, **ii**, 1.

Martin, J. P. (1957): 'Social Aspects of Prescribing', London.

Medical Research Council Report for 1957-58 (1959): H.M. Stationery Office, London.

Nuffield Provincial Hospitals Trust (1961): 'Fifth Report', London.

Peterson, O. L., *et al.* (1956): *Amer. J. med. Educ.*, **31**, No. 2, Pt. 2.

Proceedings of the Royal Society of Medicine (1961): **54**, 443.

Report of the Committee on Prescribing Costs (1959): H.M. Stationery Office, London.

Report of the Joint Working Party on Medical Staffing Structure in the Hospital Service (1961): H.M. Stationery Office, London.

Report of the Maternity Services Committee (1959): H.M. Stationery Office, London.

Report of the Royal Commission on Doctors' and Dentists' Remuneration (1960): H.M. Stationery Office, London.

Report of the Scottish Committee on Prescribing Costs (1959): H.M. Stationery Office, London.

Rutstein, D. D. (1961): *Lancet*, **i**, 498.

CURRENT THERAPEUTICS

CLXVI.—NEUROPSYCHOLOGICAL ASPECTS OF HYPEROREXIA AND ANOREXIGENIC AGENTS

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ALTHOUGH in many cultures obesity is equated with physical attractiveness and prosperity, such has not been the case, at least for several generations, in most Western societies. More recently, obesity, in addition to being considered cosmetically undesirable, has been recognized to be closely correlated with a reduced life expectancy in general and a number of degenerative disorders in particular. In spite of good medical justification, and perhaps even better statistical support for avoidance or treatment of obesity, the warnings of physicians and actuaries have been largely ineffectual; the general public is often (although only temporarily) more impressed by flamboyant claims on behalf of various proprietary remedies, alleged to make weight reduction painless and rapid.

The relationship between excessive food intake and body weight is recognized by all, with the exception of many of the obese. Food consumption is one of the responses to a basic drive for survival and is believed to be principally initiated by hypothalamic centres concerned with satiety and appetite. It is evident, however, that many other brain regions participate in the regulation of appetite and that its integration into the behavioural pattern of the individual results from the activity of various neuronal circuits reciprocally influencing each other at different levels of the neuroaxis. Any discussion of obesity and the action of anorexigenic agents therefore requires consideration of the neurological and psychological factors influencing food consumption.

GENERAL CONSIDERATIONS OF OBESITY

To be acceptable in the light of current concepts, deliberations regarding the etiology of obesity must be predicated on the thesis that the deposition of body fat represents conservation of whatever caloric intake is in excess of output. The public, nevertheless, steadfastly clings to the concept of immutable genetic or endocrine disorders as the main cause of obesity, simultaneously blithely ignoring the laws of conservation of energy. Whilst it is true that hyperorexia or hypometabolism may have inherited neuropathic or even hormonal origins, experience indicates that this is rarely the case. Similarly, an acquired neurological lesion seldom appears to be the primary stimulus for overeating, nor is it commonly a significant factor

causing hypometabolism. Instead, there is usually found an abnormally high caloric intake without evident organic cause.

We have already indicated the existence of cultural differences as regards the desirability of plumpness; other environmental factors, which may also be referred to as 'cultural', may be peculiar to a household as well as to a nation. Thus, pride in culinary skill, the belief that a fat child is a healthy one, or that obesity is an advertisement of superior economic status, may lead to the habitual overfeeding of an entire group with consequent 'familial' (or 'social') obesity. In the indigent segment of the population, economic considerations may play a significant role in obesity since the least costly foodstuffs are often characterized by high bulk or satiety value per unit weight and cost. Further, in all economic classes the supplementation of food intake by various alcoholic beverages may make its own, sometimes very significant, caloric contribution to the problem of obesity.

Whatever the reason for excessive caloric intake, its daily repetition will ultimately condition the individual; overweight stemming from such circumstances may therefore be considered to have psychological roots. The single factor probably most often ultimately responsible for obesity, however, is emotional disturbance, which frequently leads its victims to assuage their frustrations with the pleasures of eating. A vicious cycle is created in which obesity itself may be the source of, and may perpetuate, emotional instability; this is literally 'feed-back'! Because there are innumerable causes of emotional stress at every stage of life, obesity of such origin may have its onset at any age. It should be noted that obesity is usually unrelated to intellectual capacity (its incidence among idiots is not different from that in the normal population); this should not be surprising in view of the dissociation between intelligence and emotional constitution.

Hunger may be considered a symptom bringing to attention the need for food, and should probably be classified as an unpleasant sensation activated by sensory impulses normally extinguished by feeding. Appetite, on the other hand, is a consciously pleasurable or satisfaction-affording sensation, stimulating the continued ingestion of food whether or not an immediate biological need is present.

Although appetite may be influenced by a wide variety of circumstances, its basic physiology remains somewhat obscure. Certainly, little has been accomplished with regard to explaining the remarkable stability of appetite, whether normal or increased. An 'appestat' mechanism has been postulated (Brobeck, 1960) based on the concept that regulation of food intake is achieved by either visceral stimulation (gastro-intestinal motility, secretion, and distension) or by the rate of glucose uptake by one or more cerebral 'appetite centres'. It cannot be denied that gastric motility and secretion undergo cyclical changes coinciding with or immediately preceding periods of food intake. If the latter is delayed, then visceral afferents further excite central mechanisms, reinforcing the sensation of hunger. There has not yet been adduced, however, any convincing evidence to support the hypothesis

that hunger or appetite is in any way related to alterations of glucose uptake by specific cerebral structures. Moreover, the recent observation that glucagon administration (which elevates the blood-sugar level) is associated with weight loss has raised the possibility that this hormone may be involved in the regulation of food intake (Penick and Hinkle, 1961).

ANATOMICAL AND FUNCTIONAL CONSIDERATIONS

Adjustment of caloric intake to total energy expenditures with consequent maintenance of caloric equilibrium is believed to be accomplished primarily by the integrated activity of specific hypothalamic nuclei. In the experimental animal destructive lesions of the ventromedial hypothalamic nuclei may be associated with hyperphagia and obesity, suggesting that these structures, when intact, may be responsible for the sensation of satiety. On the other hand, lesions of the lateral hypothalamic nuclei may be associated with anorexia and resultant inanition, from which it has been concluded that the lateral nuclei give rise to appetite (Anand and Brobeck, 1951).

More recent studies indicate, as might be expected, that these nuclei are not autonomous and that their influence upon feeding behaviour is dependent upon afferents from other brain areas.

The stereotactic insertion of dipolar stimulating electrodes in the medial forebrain bundle of rats has disclosed that this tract, although not occupying a critical position in basic feeding behaviour, may add motivation to it, as manifested by the overcoming of barriers (electrified grid) in order to obtain food (Morgane, 1961). The medial forebrain bundle contains olfactory, para-olfactory, striohypothalamic, and septal fibres. Routing of these fibre tracts to the hypothalamus provides one mechanism whereby the motivation arising from primitive sensations may influence hypothalamic activity related to the feeding pattern. Other sensory modalities, i.e. visual, gustatory, or tactile, pertaining to the qualities and desirability of food, mediated primarily by brain-stem nuclei, are essential for basic reflex feeding patterns. Visceral afferents (activated by gastric motility and secretion) traversing specific and non-specific sensory systems, whilst not absolutely essential for feeding reflexes, are recognized to exert stimulatory or inhibitory influences upon the hunger and appetite mechanism.

There are numerous other hypothalamic afferents which directly or indirectly transmit impulses from practically all other brain areas, but the precise functional significance of many of these fibres and tracts has not been investigated to the same extent as that of the medial forebrain bundle (Ingram, 1960). One or other of the various activities of the hypothalamic nuclei, such as temperature regulation, sexual drive, thirst, awareness, hunger, and appetite, may take precedence or be suppressed, depending upon the exigencies of the moment. This functional interrelationship implies intimate connexions between these nuclei, facilitated by their juxtaposition.

CORTICAL CONTROL

The coordination and integration of the activity of the hypothalamic nuclei and their connexions, as part of the total behavioural pattern of the individual, in normal circumstances may be largely under cortical control. The feeding mechanism in man is no exception. Primitive feeding patterns are of a primarily reflex nature, as demonstrated in decorticate or decerebrate animals and even in lower forms without an integrated nervous system. With increasing complexity of the organism, there appears a greater separa-

tion between internal and external environment; control of the former must be adjusted to compensate for, or take advantage of, circumstances and opportunities of the latter. These transactions are accomplished in part by a neural structure (cortex) capable of recognition, attention, discrimination, memory, and conditioning: attributes which are utilized to satisfy, amongst other needs, hunger and appetite. The cortical functions may differ qualitatively and quantitatively in individuals, thereby giving rise to different feeding patterns. There are also efferents, passing caudad as continuations of the medial forebrain bundle and arising chiefly from the posterior and lateral hypothalamic regions, which activate appropriate visceral and hæmodynamic changes and thereby facilitate the feeding mechanism. Finally, both clinical and experimental findings indicate some assistance to the direct neural regulation of hunger and appetite by hormonal mechanisms influenced, at least in part, by the supra-optico-hypophysial system.

It may be concluded that the feeding mechanism, although residing largely in the hypothalamus, is influenced by and in turn influences the activity of all brain regions. This integration of appetite and hunger into the total behavioural pattern is achieved by complex reciprocal modulation depending upon innumerable neuronal circuits from which emerge normal or abnormal feeding activity. Such a concept serves to emphasize the shortcomings of theories and therapies which approach the problem of obesity by consideration of only its individual aspects.

PRACTICAL CONSIDERATIONS

It is thus clear that, although obesity results directly from simple imbalance between food intake and output, its development is derived from malfunction in an exceedingly complex series of neurological mechanisms manifested psychologically by increased appetite. Since the medical aim of management of obesity is the prevention or treatment of associated disease, permanent suppression of excessive caloric intake is the only acceptable criterion of success. Certainly, restriction of caloric intake to levels below expenditures will always result in weight loss, and subsequent equalization of intake and expenditure will maintain a stable weight. Advice to limit the diet is therefore theoretically impeccable; alone, however, it takes no account of abnormal emotional drives which have been more or less satisfied by excessive food ingestion.

The major weaknesses of the innumerable and usually unnatural dietary regimens commonly recommended are their occasional nutritional (aside from caloric) inadequacy and their expense, monotony, inconvenience, and frequent unpalatability which eventually lead to their rejection. Currently, a wave of popular enthusiasm has greeted the commercial introduction of prepackaged dietary preparations, nutritionally complete except as regards caloric content and with choice limited to selection of flavours. When such preparations are prescribed without supplementation, the patient is afforded no opportunity to exceed his allowable caloric intake, and, as a result,

failure of weight reduction may be recognized by all concerned to be related to surreptitious 'cheating'. The more strongly motivated patients whose previous efforts at weight reduction have been thwarted by an unrecognized (by themselves) intake of more calories than prescribed may achieve satisfying initial success with the prepackaged low-caloric 'formula' diet. On the other hand, the essential inadequacy of the exclusively physiological approach almost invariably leads to early, if not immediate, rebellion. It is therefore customary in practice to augment the patient's resolve by frequent encouragement and to attempt to relieve the physical and psychic discomfort of deprivation by inhibiting sensations of hunger and appetite.

Attempts to control hunger and appetite may conceivably be divided into three categories: substitution of more pleasurable or relief-giving stimulus than food ingestion; distraction of attention from food desire to environment; or alteration of hunger or appetite perception so that food ingestion is no longer a primary source of pleasure or relief. The first two possibilities are likely to be impractical or socially unacceptable; the third alternative has been receiving the most attention and consists basically of attempts to reduce afferent or efferent hypothalamic stimuli or otherwise to modify central neural activity, so that hunger and appetite become suppressed.

A not uncommon approach is the supplemental prescription of non-absorbable bulky substances (e.g. methylcellulose) in order to provide gastric distension and reduce visceral autonomic influences. The rapid passage of these materials from stomach and upper intestine permits the effects of their ingestion to be of only brief duration; upon arrival in the large bowel, they may induce distressing constipation.

Another method, based upon the relationship between low blood glucose levels and hunger sensation, essays to inhibit peripheral afferent neural influences by maintenance of high normal blood glucose levels. This is attempted by frequent small carbohydrate feedings which, unfortunately, may themselves obviate the desired caloric restriction. Moreover, the attack on so limited a facet of the total problem is doomed to failure by the rapid adjustment of the appetite and hunger mechanisms to elevated blood glucose levels.

ANOREXIGENIC AGENTS

The centrally acting anorexigenic agents, which at present enjoy wide popularity, are all synthetic sympathomimetic amines and are classified as cerebral stimulants since, in large doses, those effective in suppressing appetite activate alerting mechanisms and increase psychomotor activity. There is reason to believe, however, that their anorexigenic properties need not be equated with increased psychomotor activity. In the first place, certain of these agents in anorexigenic doses may have negligible clinical arousal effects and usually have no influence on electroencephalographic activity (Himwich, 1959). Secondly, many of the more potent cerebral stimulants (leptazol, picrotoxin) have little or no anorexigenic activity; and, thirdly, the feeling of well-being that accompanies moderate central stimu-

lation might be expected to be less likely to be associated with anorexia than with increased appetite, so often characteristic of the recovery phase after an illness in which appetite has been depressed.

The manner in which the synthetic sympathomimetic amines act upon the central neurones continues to be speculative. Of the various theories proposed, most of which imply a direct or competitive action upon certain cerebral enzymes, none has been substantiated. Nevertheless, most hypotheses involve the supposition of increased or decreased activity of cerebral adrenaline or noradrenaline, now widely believed to act as neuro-humoral transmitters in subcortical areas and to be responsible for central sympathetic activity. It may be significant that the effects of the anorexigenic drugs can be attributed to increased activity of subcortical structures, wherein are found the highest concentrations of the naturally occurring catechol amines (Vogt, 1957), structurally similar to the synthetic sympathomimetic agents. One may postulate that the influence of the latter upon appetite is related to stimulation of, amongst other things, an appetite suppressant centre or of structures whose increased function displaces appetite from the stream of consciousness.

Teleologically, it is important that vegetative functions, among which appetite may be included, persist for some time after activation, lest premature subsidence result in destruction of the organism. The organization of central neurophysiological activity would appear to be biochemically orientated in that it provides for a calculated delay in activity of mono-amine oxidase, a limiting enzyme for catechol amines, in order to permit prolonged self-preservatory activity. The relative non-specificity of mono-amine oxidase may be responsible for its submaximal efficiency and therefore the more prolonged and diffuse activity of catechol and synthetic sympathomimetic amines. Paradoxically, direct inhibitors of mono-amine oxidase, which might be expected to mimic the clinical action of the synthetic amines upon appetite are, in fact, recognized to have an opposite effect in that they often increase appetite. It is possible that the mono-amine oxidase inhibitors extend the action of naturally formed serotonin, as well as that of other catechol amines, whereas the synthetic sympathomimetic agents may augment catechol amine activity alone. If these comments are pertinent, then they imply that serotonin may be more active in stimulating appetite than adrenaline and noradrenaline in depressing it. Indeed, reserpine administration, which increases cerebral free serotonin levels, is often associated with increased appetite, although one cannot exclude the possibility that this effect may be somehow related to its ataractic properties.

For reasons unknown, the anorexigenic effectiveness of all synthetic sympathomimetic amines tends to subside when administered at dosage levels which do not produce the distressing side-effects of marked diffuse cerebral stimulation. The relative ineffectiveness of anorexigenic agents alone in achieving satisfactory appetite inhibition is indicated by the enormous number of available preparations, many of which differ from one

another only by the questionable virtue of combination with other agents. Recently, it has become fashionable to combine various sympathomimetic amines with ataractic or sedative drugs in an effort to control both the psychological factors perpetuating hyperorexia and excessive psychomotor stimulation by anorexigenic agents. Nevertheless, there is reason to believe that partial blocking of afferent impulses to the hypothalamus and cortex by

Anorexigenic amine	Recommended daily dose (mg.)	Psychomotor stimulation	Anorexigenic activity	Also offered combined with
Methylamphetamine	10 to 30	5+	4+	Amylobarbitone Butobarbitone Pentobarbitone Phenobarbitone Reserpine Thyroid Methylcellulose Pectin cellulose Trace minerals Vitamins
Dexamphetamine	15	3+	5+	All above, and: Quinalbarbitone Methapyrilene Meprobamate Prochlorperazine Aloin Atropine Theobromine
Lævo-amphetamine	15 to 30	1+	1+	
Racemic amphetamine phosphate (Amphetamine phosphate U.S.N.F.)	15 to 30	3+	4+	
Phenmetrazine	75	1+	4+	Trace minerals Vitamins
Diethylpropion	75 to 100	0	1+	
Phenylpropanolamine	100 to 150	0	0	Thyroid Vinbarbitone
Phentermine	15 to 30	1+	2+	

TABLE I.—Anorexigenic preparations currently available.

psychotherapeutic agents (although representing a superficially reasonable approach to the emotional background of increased appetite) may be as transitory as the anorexigenic activity of the sympathomimetic amines.

Table I lists the principal amines used for appetite suppression, as well as other drugs often employed in combination. In addition, several preparations employ mixtures of two or more amines, and various amines are available in 'sustained release' form. In view of the difficulty in developing an objective design for estimation of the relative effectiveness of these various preparations, the evaluation presented in the table rests solely on

short-term clinical impressions. The wide individual variability both in responsiveness to anorexigenic activity and in psychomotor stimulation is well recognized. Moreover, as we have emphasized, psychogenic influences play an important role in the food consumption of suitably receptive subjects so that even placebos, forcefully proposed and enthusiastically received, may by suggestion alone induce temporary suppression of appetite and therefore weight reduction. In addition, the ritualistic and ceremonial aspects of multiple self-medication maintain at the conscious level the purpose of the prescribed routine, i.e. restriction of food intake.

CONCLUSION

It may be concluded that transitory reduction of weight may not infrequently be accomplished with any form of therapy, particularly when prescribed to a strongly motivated subject. There is no convincing evidence that more than an insignificant proportion of obese patients ever achieves permanent suppression of excessive caloric intake; ultimate failure is due to our inability to control the neuropsychological mechanisms responsible for hyperorexia. It becomes increasingly apparent that the pathophysiology of obesity is closely allied to the complex problems underlying the basic psychological and neurophysiological disturbances occurring in narcotic addiction, chronic alcoholism, and tobacco habituation. It would seem that in all these disorders the final common pathway is preoccupied with the emotional aspects of pleasurable stimuli and is often indifferent even to those stimuli which normally arouse an urge for self-preservation. In this regard, it may be significant that in animals the implantation of electrodes in various subcortical structures, stimulation of which induces pleasurable sensations, is soon followed by remarkably persistent repetitive self-stimulation to the point of complete exhaustion, having at least an external similarity to human obsessive-compulsive behaviour (Olds, 1956).

When it is recalled that excessive appetite may reflect a need for pleasurable sensation or relief from psychic discomfort, the obese patient's reluctance to repress appetite should not be surprising. Its successful inhibition, if achieved without satisfactory substitution, may conceivably produce habituation or neurosis more incapacitating than those of which obesity may be a symptom and may be more hazardous than the medical consequences of obesity itself.

References

Anand, B. K., and Brobeck, J. R. (1951): *Yale J. Biol. Med.*, **24**, 123.
Brobeck, J. R. (1960): 'Handbook of Physiology. Section I. Neurophysiology, Vol. II', Baltimore, p. 1197.
Himwich, H. E. (1959): 'The Effect of Pharmacologic Agents on the Nervous System', Baltimore, p. 356.
Ingram, W. R. (1960): 'Handbook of Physiology. Section I. Neurophysiology, Vol. II', Baltimore, p. 951.
Morgane, P. J. (1961): *Science*, **133**, 887.
Olds, J. (1956): *Scient. Am.*, **195**, 105.
Penick, S. B., and Hinkle, L. E., Jr. (1961): *New Engl. J. Med.*, **264**, 893.
Vogt, M. (1957): *Brit. med. Bull.*, **13**, 166.

CALLING THE LABORATORY

XXII.—LABORATORY TESTS IN THE INVESTIGATION OF INFERTILITY

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It must be emphasized that the investigation of infertility begins in the consulting room, with history-taking and physical examination. Relatively few laboratory tests are involved in the routine investigation but a wide variety may be desirable in rare cases.

SEMINAL ANALYSIS

This is a basic test which should be omitted only in special circumstances. When, for religious or other reasons, a man is unable to provide semen for analysis, the post-coital test may be used as a substitute and, if satisfactory, may be taken as *prima facie* evidence of reasonable semen production.

Techniques and the elaboration of results differ in various laboratories, but in all cases the important data to be obtained are the volume of the ejaculate, the sperm density, the proportion of abnormal sperms and an estimate of spermatozoal activity. The following instructions for the patient are necessarily dogmatic since it is not possible to argue the matter in detail here.

The patient should be asked to produce a masturbation specimen into a clean, dry screw-capped glass or plastic jar (which should be slightly warmed in cold weather, to protect against 'temperature shock') after a fixed period of abstinence (usually stated as three to five days). The time of production should be recorded. The specimen should be examined within three hours and, since viability determinations also require examination of the specimen several hours later, it is usual to insist that the specimen be in the laboratory during the morning. Except when it is merely a question of confirming azoospermia, specimens cannot be sent through the post.

What constitutes a normal seminal specimen is still to some extent debatable: the ejaculate volume averages about 3.5 ml., the minimal sperm density compatible with normal fertility is probably 20 to 30 millions per ml., provided the activity is of a high order, and the proportion of abnormal sperms should not exceed 40 per cent. It is technically very difficult to make accurate measurements of sperm activity and estimates of very varying reliability are used. In the intermediate range these are of doubtful significance though quite meaningful at either end of the scale.

If the first specimen is unsatisfactory, it is a wise rule to have two more examined since some men show great variation in different ejaculates.

TESTICULAR BIOPSY

Although studies of testicular histology in cases of defective spermatogenesis have certainly increased our knowledge of testicular disorders, biopsy in the routine investigation of infertility should be strictly limited since it is rarely that the information obtained leads to the institution of rational and effective therapy. It is mostly reserved for cases of azoospermia since the demonstration of normal spermatogenesis then indicates an obstructive etiology which might be amenable to surgical treatment.

The biopsy fragment should be fixed immediately (the pathology laboratory should be consulted as to which fixative is preferred).

HORMONE EXCRETION STUDIES IN MEN

These have no place in routine investigation but determination of urinary 17-ketosteroids and gonadotrophins may be helpful in the investigations of hypogonadism. Exact 24-hour urine specimens, collected without preservative and delivered fresh to the laboratory on the morning of completion of collection, are required. Although 17-ketosteroid determination is now carried out in many clinical biochemical laboratories, only a few can undertake gonadotrophin estimations.

Determination of 17-ketosteroids is a purely chemical procedure.

It involves hydrolysis and extraction of the urine, separation of the 'neutral fraction' and development of colour either by the Zimmermann or the Pincus reagent. From the amount of colour, read in a spectrophotometer, the quantity of steroid can be calculated. It reflects the 'male hormone' output of testes and adrenals and if less than about 8 mg. per twenty-four hours is confirmatory of hypogonadism.

The measurement of *urinary gonadotrophins* is technically far from satisfactory. The protein hormones in the urine are extracted by adsorption and precipitation techniques and are then estimated by bio-assay, the usual test object being the weight of the uterus of the immature mouse. One 'mouse unit' is generally defined as the amount of hormone which will cause a 100 per cent. increase in uterine weight as compared with that of the control untreated mice. It is not normally possible to demonstrate a *decreased* output of gonadotrophin though differentiation between normal and increased outputs is possible. Hypogonadism with raised urinary gonadotrophins indicates primary testicular failure, the associated infertility therefore being untreatable. With hypogonadotrophic hypogonadism, on the other hand, there is some chance of successful treatment.

POST-COITAL TEST

This is scarcely a 'laboratory test' since, requiring only a microscope, it should be performed by the clinician in the examination room. Although it is the simplest of the special investigations of the female, it is the one which most often fails to give a normal result, and yet which is most often omitted. It has to be carried out during the 'fertile phase' of the cycle, close to the probable time of ovulation; a negative result at other times has no significance. The couple are instructed to have intercourse in the night

or morning before the test is performed and a time interval of up to eighteen hours or so is quite permissible. A speculum is inserted into the vagina to expose the cervix and some of the cervical mucus is aspirated from within the cervical canal and transferred to a slide. In the ideal result, the mucus is copious, clear, watery, draws out into a long thread (*spinnbarkeit*) and, under the microscope, is seen to contain large numbers of highly active spermatozoa.

If the test has been carried out at the correct stage of the cycle, faulty mucus production must be assumed if clear, copious, well-invaded mucus is not found. If the mucus is of correct consistency and quality, but few or no spermatozoa are seen, while reference to the husband's seminal specimen shows no fault in sperm production, defective coital technique may be presumed.

Invasion test.—This extension of the post-coital test is sometimes of help in analysing faulty results. To perform it, a drop of cervical mucus and a drop of semen are placed side by side on a slide and covered by a coverslip so that a mucus-semen interface is produced. The progress of spermatozoa into the mucus (or its failure) can then be observed under the microscope. The husband's semen can also be tested against mucus of known receptivity, whilst the wife's mucus can be tested against spermatozoa of known invading capacity.

TESTS FOR THE OCCURRENCE OF OVULATION

Apart from direct observation of its occurrence (which has been made by culdoscopy but obviously is not a practical routine procedure) ovulation can only be presumed through indirect evidence. This can be obtained from basal temperature records, premenstrual endometrial biopsies (the biopsy fragment should be fixed immediately), and studies of changes in the vaginal smear and cervical mucus. Procedures depending upon the detection of hormone changes in the urine by simplified methods, or of glucose in the cervical mucus, appear to be unreliable.

Daily vaginal smears are required for detection of ovulation time. The patient can be instructed to take her own smears and to fix them in an alcohol-ether (equal parts) mixture. They can be delivered to the laboratory either daily or weekly. They are usually stained in a differentiating stain (such as Shorr's). Clearly the procedure is somewhat cumbrous. At ovulation, there is usually a sharp rise in the proportion of epithelial cells with pyknotic nuclei, followed by a fall and the sudden appearance of numerous leucocytes. Obviously, vaginal smear studies are useful only in the absence of inflammation and, moreover, they may be vitiated by the occurrence of coitus.

The observation of cervical mucus changes does not require the cooperation of the laboratory. As previously stated, at the time of ovulation the mucus is characteristically copious, watery and clear. If dried on a slide, it forms striking fern-like crystals of sodium chloride. After ovulation, it

becomes tacky, cellular, less copious and no longer crystallizes. Failure of the mucus to undergo these changes suggests the non-occurrence of ovulation.

TESTS FOR CORPUS LUTEUM FUNCTION

'Progestational insufficiency' is thought to be not uncommon in infertile women, and especially in those with a history of early abortions. It may be diagnosed if the premenstrual endometrial biopsy shows an inadequate degree of secretory development for the stage of the menstrual cycle. The vaginal smear may also be helpful: a pyknotic index above 20 per cent. during the luteal phase is suggestive of luteal insufficiency. Urinary pregnanediol estimation, though giving information on progesterone production, is too time-consuming to be of routine use and the same is true of œstrogen estimations. These chemical procedures require repeated (for the most accurate work, serial) 24-hour urinary collections.

MISCELLANEOUS TESTS

Women with oligo- or a-menorrhœa, especially if associated with hirsutism, should have *urinary 17-ketosteroid estimations* since in many cases adrenal hyperplasia will be found and may respond satisfactorily to corticosteroid therapy. Figures in excess of 15 mg. per twenty-four hours probably imply adrenal overactivity and warrant a trial of therapy. If the 17-ketosteroid excretion is not raised, evaluation of ovarian size—by gynæcography (pelvic x-ray examination after the induction of a pneumoperitoneum) or culdoscopy—may be desirable to exclude the Stein-Leventhal syndrome.

Sex chromatin determination (for example by means of buccal smears) or actual chromosome counts may be valuable in hypogonadism in both sexes. Thus, the finding of positive chromatin in an azoospermic male would lead to the diagnosis of Klinefelter's syndrome; and of negative chromatin in an amenorrhœic female, gonadal dysgenesis or male pseudohermaphroditism. These conditions hold out no hope for fertility. The technique for buccal smears is to have the patient scrape the inside of the cheek with the fingernail which is then rubbed momentarily on a slide to deposit the cells. The slide must be fixed immediately in alcohol-ether mixture and can later be stained with suitable nuclear stains. Chromosome studies can be made on blood, bone marrow or skin biopsies. These are cultured for a short time in the presence of colchicine (which arrests mitosis at metaphase), the chromosomes are spread by treatment with hypotonic saline and the cells are fixed and stained in the usual way. High-magnification photomicrographs are used for studying the chromosomes.

Special circumstances may occasionally indicate the need for the usual pathological and hæmatological studies, or for tests of thyroid function (basal metabolic rate, blood cholesterol, protein-bound iodine and radioactive iodine tests).

PRINCIPLES OF REHABILITATION

X.—FINANCIAL INDEPENDENCE

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The third object of rehabilitation is gainful employment leading to financial independence. Re-entry into gainful employment requires:—

(i) The ability to get from home to place of work. (ii) The ability to carry out the selected job on equal terms with the other workers.

RETURN TO ORIGINAL EMPLOYMENT

The initial aim should always to be to return the disabled to their pre-accident or illness type of work and under the same employer, as they are already familiar with their own trade and because this is almost invariably easier than training them for fresh skills. There are two features which do not receive enough attention. The first is the early instillation into the patient's mind of the idea that he is going to be able to go back to work. The second, and no less important, aim is to make early contact with the employers so that they are also expecting the person back. I make no apologies for stressing these two factors since omission to carry these out may well lead to insuperable difficulties if they are undertaken after a time interval of weeks or months, since it then involves reorientating either the patient or employer or both. It therefore is most important that the patient be seen as early as possible and a provisional assessment made and the patient's cooperation solicited in planning his future.

If the problem of travelling to work arises this can be solved by the provision of a petrol or electrically propelled tricycle, as mentioned in a previous article in this series (*The Practitioner*, February 1961, **186**, 263).

If a case shows any signs of being at all difficult, it is most important for the doctor in charge to make personal contact with the people concerned and not to delegate this responsibility. Generally speaking the doctor has a far better entré to executive level than anybody else. Should the firm have an industrial medical officer on the staff, full use should be made of his valuable cooperation. It is obvious that all firms conduct the running of their departments with the object of showing a satisfactory financial balance at the end of the year, and therefore it is wrong to expect them to subsidize or carry completely somebody who cannot usefully contribute to the running of the firm. At the same time, it has almost invariably been my experience that a correct approach as outlined produces a sympathetic and helpful response. In many cases it may be necessary to seek advice from the firm on methods by which the patient's job may be modified to fit in with his disability, but it is imperative that such loose phrases as 'light work'

should be avoided as this is an entirely negative way of viewing the situation and can at best only lead to some such job as sweeping the floor or making tea. All doctors should be capable of telling the employer what a patient can do and this is what he wants to know.

ALTERNATIVE EMPLOYMENT

The next category of patient is the one who cannot return to his former employment and more suitable work must be sought elsewhere. When such work is not available, the patient and his disability must now be assessed from the point of view of training in alternative forms of work, and advice may be sought through the services of the Ministry of Labour via the disablement resettlement officer. These courses are many and varied and must be selected with a view to suitable jobs being available when the training is over; otherwise all will have been in vain. When any such rehabilitation programme has been set in motion, it is important for some responsible person to hold a watching brief and review the situation at frequent intervals to ensure that nothing has gone awry. It does not matter by whom this is done, always provided he or she has the necessary personality and insight.

SHELTERED EMPLOYMENT SCHEMES

When this has been done, there still remains a number of individuals who will be permanently, or for a long period, unfit to undertake employment under normal working conditions, or who are too substantially handicapped for competitive employment with normal people. The easiest way of dealing with these cases is through sheltered employment schemes, but each patient should be regarded as an individual challenge and every effort should be made to get them into employment under normal conditions. It is common experience that we cannot arrange for useful gainful employment to be carried out at home except in one or two highly specialized instances.

If a person has a severe locomotor disability, the question arises as to whether this can be compensated for by making more use of his brain. In this context I have in mind two contrasting cases.

One is a victim of poliomyelitis affecting the lower thoracic region downwards, but with reasonably strong upper extremities. She has been trained in book-keeping and is now managing her family and earning £12 a week.

The other is an intelligent youth who virtually stopped all schooling at fourteen but who was capable of being coached in, and passing, his 'O' level examinations and has been articled to a chartered accountant. As he cannot lift the heavy ledgers necessary to the job, it has been necessary, with the full cooperation of his employers, to arrange for the construction of a motor-powered revolving table so that the heavy lifting is avoided.

THOROUGH AND REPEATED ASSESSMENT

Finally, the value of thorough and repeated assessment cannot be overstressed. Properly handled patients who cooperate fully, often make a functional recovery far in excess of anything which could legitimately have been anticipated solely on clinical grounds.

REVISION CORNER

CAUSALGIA

THE intense persistent pain in the hand or foot which may sometimes follow injury of a peripheral nerve was first described by Paget in 1864. It was Weir Mitchell and his associates who first used the term 'causalgia' to describe the condition in the same year. A burning quality was long regarded as an invariable feature of the pain, but it is now generally accepted that this is not an essential criterion in the diagnosis. More important is the fact that the pain is always aggravated by emotional stimuli, which distinguishes it at once from all other painful syndromes associated with traumatic lesions of peripheral nerves.

ETIOLOGY

Although causalgia may occur as a result of a lesion of any nerve it is most apt to appear when there is an incomplete lesion of the median or medial popliteal nerves, or of their roots or branches. Sometimes there may be multiple nerve lesions. It rarely, if ever, occurs after complete division of a peripheral nerve and is a rare complication of an incised wound. It is most commonly encountered with injuries to the proximal part of a limb and when there is a stretch injury, as occurs when a high-velocity missile passes close to a nerve. Injuries of this type may cause various degrees of damage to the axons as well as degeneration of their myelin sheaths; moreover, it has been shown that in these circumstances an artificial synapse may be formed which allows impulses to pass between the various nerve fibres at the level of injury.

PATHOGENESIS

There is as yet no theory of the pathogenesis of causalgia which adequately accounts for all that is known about it. The most satisfactory theory we have is based upon the well-known observation that sympathetic block will relieve the pain in most cases. It is thought that the stretching of the nerve which usually occurs at the time of injury breaks down the insulation of the nerve fibres. In this way an artificial synapse is established between the efferent sympathetic fibres and afferent sensory fibres. Impulses passing down the sympathetic fibres are thus 'short-circuited' to the sensory somatic fibres via which they travel both centrally and distally. The distally travelling (antidromic) impulses are thought to cause the release at the periphery of a histamine-like substance. The latter is considered either to reduce the threshold of sensory stimulation or to set up centripetal impulses in the sensory fibres which summate with the centripetal impulses arising directly at the artificial synapse.

On the basis of this hypothesis sympathectomy would relieve the pain by abolishing all the efferent impulses which are travelling down the sympa-

thetic fibres and which are also gaining access to the adjacent somatic fibres via artificial synapses. It also accounts for the frequency of involvement of the median or medial popliteal nerves, as these nerves carry most of the sympathetic fibres to the hand and foot respectively. The remainder are carried chiefly by the ulnar and lateral popliteal nerves. During waking hours efferent impulses are constantly streaming down sympathetic fibres; the fact that the flow is increased by a wide variety of physical and psychical stimuli would account for the exacerbation of causalgic pain when such stimuli are applied.

CLINICAL FEATURES

The pain of causalgia is severe, spontaneous and persistent. It usually has a burning quality, may spread beyond the territory of the injured nerve or nerves and is invariably aggravated by both physical and emotional stimuli. Due to the general lowering of the threshold for all sensory stimuli the lightest touch or vibration will aggravate the pain, and so the patient carefully avoids all movements of the affected limb. Many sufferers seek relief from their pain by the use of cold wet applications to the hand or foot. The aggravation of the pain by psychic stimuli is striking, particularly when these evoke excitement or apprehension. Because of this some patients will try to isolate themselves from all stimuli, and even complain they cannot read anything which excites them. There is, however, no good evidence to support the contention that sufferers from causalgia are of unstable temperament. The pain is always felt in the hand or foot and rarely radiates into the forearm or leg. In the majority of cases it appears within twenty-four hours of the receipt of the injury. Thereafter it usually becomes worse during the next few hours or days and may persist for many months if untreated. It does not usually prevent sleep, however, unless the environment is disturbing, and even after a period of many months slow spontaneous improvement begins to occur.

The occurrence of so-called trophic changes is a variable feature. In some cases there may be smoothness and shininess of the skin, stiffness of joints, wasting of muscles, osteoporosis and atrophy of the pulps of the fingers. Even so, these are phenomena which are attributable as likely as not to disuse rather than a primary feature of the lesion itself. Sometimes there may be increased warmth and sweating of the skin of the affected part, but such changes again are very variable and may even be absent.

Testing of motor and sensory functions is difficult because of the patient's apprehension of any form of stimulus. The degree of motor involvement tends to be variable. Often there is little or no loss of power, and even when there is severe paralysis initially some degree of recovery will occur. Sensory changes are even more variable. Some patients exhibit extreme hyperæsthesia and hyperalgesia of the hand and foot. When, however, sensory examination is possible varying degrees of impairment of appreciation of pin-prick and light touch will be found in a part or the whole of the sensory distribution of the affected nerves.

TREATMENT

In early cases medical treatment may be given a trial. This consists of the use of sedatives and analgesics in combination with moist local applications at a temperature which the patient finds most soothing. Immobilization of the limb should be avoided but passive movements can be carried out with advantage if they can be tolerated.

Medical measures can sometimes be effectively combined with procaine block of the sympathetic, but in the treatment of any severe case of causalgia sympathectomy, with or without excision of the damaged area of nerve, is the method of choice. Most patients obtain striking relief in this way provided that they are carefully selected. Before deciding upon this operation it is essential to try the effect of procaine block of the sympathetic. This usually results in relief from pain for from one to three hours; if it does not do so, then sympathectomy is not advisable. In the arm the operation of choice is pre-ganglionic sympathectomy in which the second and third thoracic ganglia are isolated by dividing the white rami communicantes to each ganglion and the sympathetic trunk below the third ganglion. In the leg a comparable pre-ganglionic sympathectomy is carried out by removing the first, second and third, or second, third and fourth lumbar ganglia. By the use of these methods relief from the pain of causalgia is usually complete or substantial. Rarely there may be some return of pain after operation, whilst hyperæsthesia and hyperalgesia may sometimes persist.

M. J. PARSONAGE, M.B., F.R.C.P.
Consultant Physician, Neurological Department, General Infirmary, Leeds.

NOTES AND QUERIES

Treatment of Carcinoma of the Breast

QUERY.—What are the indications for using (a) stilbœstrol and (b) testosterone in metastatic carcinoma of the breast? How does the giving of stilbœstrol rationalize with performing oöphorectomy in certain cases; a procedure whereby one is removing the source of œstrogens?

REPLY.—It would be unwise at the present time to answer this question too dogmatically or to rationalize too glibly, for no-one really knows exactly what is the endocrine influence on carcinoma of the breast. For some time now it has been taught that œstrogen—endogenous œstrogen, at any rate—is an important factor in the etiology of breast cancer; hence oöphorectomy in premenopausal women. Then the idea developed that if you 'alter the endocrine environment' this may slow down the malignant progress or even lead to remission. Thus it would be logical to androgenize the premenopausal woman. Simple androgens such as testosterone propionate, however, have proved disappointing in practice, only about 20% of cases showing any relief, particularly perhaps in regard to the pain of osseous metastases. On the other hand, certain anabolic agents, such as nandrolone (nortestosterone phenyl propionate), seem to have given relief and temporary remission in about half the cases treated and have been relatively free of virilizing effects. In a double-blind trial with 2-methyl-dihydrotestosterone and testosterone propionate conducted at the Mayo Clinic, approximately 50% of the patients showed dramatic regression of the condition on

the androgen analogue, which was significantly greater than that obtained with the pure androgen. This suggests that certain androgen (and possibly even progesterone) analogues may be direct anti-cancer agents quite apart from their property of changing the endocrine milieu.

With regard to the œstrogen (stilbœstrol) treatment of metastatic breast cancer it should be reserved for post-menopausal women, and the longer past the menopause the greater the tendency for gratifying results to occur. If given to premenopausal women there is considerable danger that the condition may be exacerbated and become fulminant as it often does in pregnancy. Nevertheless there are reports of remission in premenopausal women treated with œstrogens, just as there are reports—and indeed, considerably more—of post-menopausal women responding dramatically to androgens.

Oöphorectomy is an important procedure in all premenopausal patients, for *endogenous*, as opposed to *exogenous*, œstrogens almost certainly play a predominant part in the etiology of breast cancer. Indeed adrenalectomy and hypophysectomy are designed further to remove the sources of endogenous œstrogens, and even these operations are not totally successful in achieving this aim, for significant quantities of urinary œstrogens are found after all these operations.

To summarize, then, in answer to the last part of the question, oöphorectomy is performed to remove the principal source of (?) cancer-producing endogenous œstrogen. Stilbœstrol is administered after the menopause, possibly to change the endogenous endocrine milieu, which by that time is neither masculine nor feminine, but 'neuter', or, possibly to inhibit over-production of pituitary gonadotrophins, which may be potentially carcinogenic.

P. M. F. BISHOP, D.M., F.R.C.P.

Treatment of Ménière's Disease

QUERY (from a reader in India).—I have a female patient, aged 50, who has been nearly completely deaf in the right ear since a severe attack of typhoid fever in 1954. There is no more than 20 per cent. acuity. In 1950, for seven weeks she became intolerant to noise and vibrations and music was distorted. Again in 1955 she had a similar attack lasting for four months. This time dizziness and nausea were added.

In 1960 she went to the United Kingdom via Canada by ship. She developed a cold and sinusitis and this started her Ménière's symptoms again. She was advised in Canada to take vitamin B complex and phenobarbitone. It was noted that excitement aggravated the deafness. Matters improved until she landed in India when all the symptoms of deafness, dizziness and nausea returned. It has been noted that there is a 'chord' of sound in the ear associated with the pulse beat. In January this year she had two dizzy spells after which the deafness gave way to acute hearing lasting in one case a few hours and in the other five days. Vitamin A in large doses had been prescribed in Canada but never given. This was tried with no success.

On the assumption that Gopalan's syndrome is common and that a nerve lesion was present I have given large doses of vitamin B_6. Two days after this was started she heard again clearly and to date is well.

Is there any more that can be done, for I am fairly sure the cure will only be temporary?

REPLY.—The symptoms sound as though the patient has endolymphatic hydrops, or Ménière's disease, although from the description it is not quite clear which ear was originally affected. In such cases when the hearing is badly affected a series of injections of histamine diphosphate will sometimes help. It may be given as a subcutaneous injection—1 mg. of histamine diphosphate in a 1 ml. ampoule twice weekly—or in more severe cases the patient may be admitted to hospital and given histamine in an intravenous drip, the dosage being 2.5 mg. of histamine diphosphate in 250 ml. of normal saline. This is given daily over a period of half-an-hour for five days.

The basic treatment for endolymphatic hydrops is to keep to a low-sodium diet and a somewhat limited fluid intake. In a hot climate the fluid restriction need not be so great, particularly if the patient can be careful about his sodium intake. Probably 4 pints (3.5 litres) of fluid would be sufficient.

TERENCE CAWTHORNE, F.R.C.S.

Diuretics in Diabetes Mellitus

QUERY (from a reader in Yugoslavia).—Is there any great risk in giving strong diuretics, such as hydrochlorothiazide, to patients with diabetes mellitus? If there is such a risk, is this due to loss of sodium or some other anion or cation? Could such a loss induce cardiac failure?

I ask these questions because two of my patients have recently died of heart failure about the tenth day on hydrochlorothiazide. Both of them were receiving this treatment because of hypertension. The urine of the first patient was not examined for glucose, but the urine of the second (a woman aged 60) contained a large amount of sugar, but no acetone. The blood sugar was 230 mg.%, and she was put on 90 units of insulin a day. In an attempt to control the heart failure both patients received 'cedilanid'.

REPLY.—There is no greater danger in giving oral diuretics to patients with diabetes than to others provided the diabetes is properly controlled. It would clearly not be wise to give these drugs to patients who were severely ketotic. It seems probable that in both the patients quoted the cause of death was unrelated to diabetes.

D. A. PYKE, M.D., M.R.C.P.

Fungus Infections of the Toe-Nails

QUERY.—What is the most effective way of treating fungus infections of the toe-nails?

REPLY.—Dermatophytes live in dead tissue: toe-nails are very dead. Locally applied antifungal preparations cannot penetrate the nail to a depth sufficient to do any good. Griseofulvin, given by mouth, reaches and settles in those cells destined to die and become keratin in the earlier, viable phase of their life. Clearly the concentration of the drug in the keratin depends upon the rate of outgrowth of the nail: and toe-nails grow so slowly, taking about one year to grow their whole length. This explains why griseofulvin only rarely fails to cure a fungus infection of the finger-nails but will cure, perhaps, only 10% to 15% of toe-nail cases. Curiously, perhaps, some nails will respond admirably, whilst others, in the same patient, remain grossly infected. Sometimes all the nails of one foot are cured whilst those on the other are untouched.

I would suggest a trial of griseofulvin, 0.5 g. twice a day, for as long as improvement is maintained. Cure would take twelve months. No improvement in any of the nails after three months is an indication for avulsion of the lagging nails, the drug still being taken by mouth. After avulsion, nails grow faster until their full length is reached. Even with avulsion cure is still not certain, but the chances are high.

DAVID I. WILLIAMS, M.B., F.R.C.P.

Convergent Strabismus

QUERY.—I should be grateful for ophthalmological advice on a boy aged 4½. He has a right convergent strabismus, first developing a year ago. Six months ago, following an attack of bronchitis, it became much worse, glasses were prescribed, and the left eye was covered. He now uses either eye, but surgery has been advised. What are the factors which the surgeon takes into account in deciding to operate (i.e. are all cases operated on now?) and what would the prognosis be if operation were refused?

REPLY.—The factor which makes surgery imperative in the treatment of this child is the presence of an angle of squint even when glasses are being worn, and it is presumed that the refractive error has been fully corrected. The angle of squint means that the child cannot use both eyes together without seeing double, and, unless the angle of squint is abolished, the child will take steps to avoid double vision by the development of suppression of one eye and eventually amblyopia.

If there were no angle of squint with glasses in place, and a convergent squint only when the glasses were removed, such a child would not require surgery and would be able to continue to lay down the pathways for binocular vision and consolidate each stage in development.

STEPHEN J. H. MILLER, M.D., F.R.C.S.

Thomsen's Disease and Heredity

QUERY.—A patient of mine, aged 21, suffers from Thomsen's disease. This does not cause him much disability and he is greatly relieved by taking procainamide, which he does regularly and with appropriate blood supervision. He wishes to marry his first cousin. There is no family history traceable of any other case of Thomsen's disease.

(1) Is it possible for you to tell me the mathematical chances of a child of this marriage having Thomsen's disease?

(2) Would it be reasonable for him to be sterilized and for the couple to adopt children? He has suggested this himself.

(3) Are any children of the marriage who are born with the disease likely to be more severely affected than he is?

I understand that there is no particular danger to life with this disease other than accident-proneness and so on.

REPLY.—(1) Thomsen's disease in Dr. Thomsen's own family, and in most others since, is inherited as an autosomal dominant (Thomasen, 1948). Provided that the patient's cousin is unaffected—and it would be wise to make sure of this—the chance of a child being affected is the one in two chance that the patient will transmit the dominant gene to any particular child.

(2) It would not be unreasonable for the couple to adopt children rather than have any of their own, but the decision is best left to the patient. Sterilization is perhaps not appropriate now that reliable methods of contraception are available.

(3) Probably not. It is generally accepted now that Thomsen's disease is distinct from dystrophia myotonica.

Reference
Thomasen, Eivind (1948): *Op. dom. Biol. hered. hum (Kbh.)*, 17.

C. O. CARTER, B.M., M.R.C.P.

Sterilization of Rubber Gloves

QUERY (from a reader in South Africa).—Is it safe to sterilize rubber gloves with cetrimide solution by leaving them to soak for twelve hours? The gloves are used for vaginal examinations at my surgery, immediately after which they are washed under the tap, filled with the solution and left to soak, the procedure being simpler than boiling and the gloves lasting longer. What strength of solution would you recommend?

REPLY.—Rubber gloves can be sterilized with certainty only by steam under pressure but if this is not possible in the circumstances other methods must be adopted. It should be recognized, however, that any other method runs the risk of being imperfect. Most vegetative organisms are not difficult to kill with disinfectants but the possibility of the presence of spores makes the whole problem of chemical disinfection much more difficult. There are only two chemical disinfectants which are active against spores: chlorine and formaldehyde. Since gloves used in vaginal examinations run some risk of being contaminated with Clostridia it would be essential to use one of these two substances and cetrimide cannot be regarded as satisfactory. How gloves would stand up to sterilization by either of these substances I do not know and can only suggest that they be tried. A concentration of 8% formaldehyde or 2% 'Milton' for twenty-four hours would probably be effective.

W. D. FOSTER, M.D.

A Problem of Stature

QUERY.—I have a patient, a lady of 21, who is very anxious to join the women's police. Her height is 5 feet 4½ inches (1.63 metres), and the required height is 5 feet 5 inches (1.65 metres). She wants to know how she can increase her height by ½ inch, so as to meet this requirement. She is healthy in every respect. I should be most grateful for advice.

REPLY.—It is unlikely that at this young lady's age further growth can be expected. I fear that the only suggestion I can make is rather disarming in its simplicity, but since only half-an-inch separates her from her ambition she might succeed by subjecting herself to a vigorous stretching by traction on the lower limbs after spending a long night—better still perhaps twenty-four hours—in bed and applying for measurement as soon as possible after rising. Her actual height will not be increased but she may temporarily achieve the necessary additional length which for the present purpose is a distinction without a difference.

SIR ADOLPHE ABRAHAMS, O.B.E., M.D., F.R.C.P.

Epilepsy and Driving

QUERY.—Arising out of the query and reply on driving with a previous history of epilepsy (*The Practitioner*, June 1961, p. 792):—

(1) What is the medico-legal liability of a doctor issuing a certificate of fitness and that of the insurance company in a hypothetical case of serious accident, a fit having occurred?

(2) What are the medico-legal aspects of liability when epilepsy is pleaded as a cause of an accident, no previous history being known or revealed?

REPLY.—(1) It is impossible to give a precise answer to a hypothetical question of 'medico-legal liability' as each case must be judged on its full facts and circumstances as adduced by the evidence. For the purpose of this reply it is therefore assumed that the reader wishes to know whether the doctor who made the original inquiry on this subject is likely to be sued for damages for alleged negligence or accused of unlawful certification if he followed Dr. Johnson's advice and decided that he could conscientiously certify his opinion that the patient concerned was fit to drive a private vehicle, but the patient had subsequently been involved in an accident caused by an attack of grand or petit mal while driving.

On these facts the doctor would not have any legal liability for the accident, *provided* that he has certified his opinion in good faith and after careful clinical assessment of all the factors involved, including the criteria set out in the last paragraph of Dr. Johnson's admirable reply.

The decision to certify fitness to drive is really one of professional conscience rather than legal obligation and there are some doctors who might prefer to follow the stricter rule recommended by the World Health Organization in 1956 that persons who gave a history of any form of epilepsy should not be permitted to drive. Perhaps a useful test might be 'would I be happy to allow myself or my family to be driven by this patient in all traffic conditions likely to be met in this area or elsewhere?'.

(2) This also is a hypothetical question but the answer is clearly that a doctor cannot have any legal liability for an accident involving a patient in a legal claim or prosecution who pleads that it was caused by epilepsy, no previous history being known or revealed. In such circumstances it is presumed that the patient would not have sought any certificate of fitness to drive from his doctor unless it were because of some other disability.

ALISTAIR FRENCH, M.R.C.S., L.R.C.P., D.I.H.

Kerosene (Paraffin) Poisoning

DR. J. U. SHAH, Thomson's Falls, Kenya, writes:—'In his excellent article on "First Aid Treatment of Poisoning" in the July issue (p. 29) Dr. Rex Tattersall does not mention kerosene (paraffin) poisoning. In my small practice I have seen more cases of kerosene poisoning than any other. It is no uncommon sight to see the desperate parents rushing to the surgery with their child who has swallowed kerosene. Although the results are not usually either fatal or serious, I feel that kerosene deserves inclusion in any article on poisoning'.

DR. TATTERSALL writes:—'I have read Dr. Shah's note with much interest. A physician in Northern Ireland has made the same comment to me—that paraffin poisoning is the commonest poisoning he sees in a rural district, particularly in children.

In view of the fact that there is no specific therapy, and that it is rare for much to have been swallowed, the treatment of emesis and gastric lavage is the same as for most other forms of poisoning'.

PRACTICAL NOTES

Treatment of Gall-stones

IF radio-opaque gall-stones are found quite incidentally on x-ray of the abdomen for another suspected or known condition, and the symptoms are clearly caused by this condition, it is customary not to advise their removal, according to A. J. Harding Rains, in a lecture on 'Gall-Stones' which he delivered recently at the Royal College of Surgeons of England (*Annals of the Royal College of Surgeons of England*, August 1961, **29**, 85). On the other hand, operation should be considered in cases in which large faceted stones are seen, 'for it is probable that these are filling out a gall-bladder now devoid of function'. In such cases cholecystography should be carried out and, if the gall-bladder is proved to be non-functioning, cholecystectomy should be advised. The most difficult cases are those in which radiolucent stones are revealed by cholecystography carried out in the course of investigation of a patient with subacute gastro-intestinal symptoms in the upper abdomen. It is noted that cholelithiasis is 'sometimes part of a group of intra-abdominal conditions such as hiatus hernia, duodenal ulcer, chronic appendicitis and diverticulitis' and 'only after a reasonable exclusion of the different diagnoses can cholecystectomy be advised'. If investigation by cholecystogram or intravenous cholangiogram proves definitely that gall-bladder function is impaired, 'one may more confidently advise cholecystectomy'. The position with regard to acute cholecystitis is summed up as follows. 'A resolute ten-day course of penicillin and streptomycin, or of chloramphenicol or tetracycline may be given . . . As the condition subsides . . . one plans for confirmatory x-ray investigation and cholecystectomy eight to twelve weeks later'. In a fulminating case, however, in which increasing pain, tenderness and pulse imply gangrene of the gall-bladder, local peritonitis, abscess formation or a more general spread, an emergency operation should be performed.

Treatment of Diabetes Insipidus

FOLLOWING reports indicating that thiazides act as antidiuretics in experimental and clinical diabetes insipidus, B. Calesnick and Sophie A. Brenner (*Journal of the American Medical Association*, July 1, 1961, **176**, 1088) investigated the use of hydrochlorothiazide in a 45-year-old woman who had previously received continuous treatment for idiopathic diabetes insipidus for more than six years. For over four years her condition had responded to injections of vasopressin tannate but recently their action had become unpredictable and side-effects troublesome. An initial daily dosage of 200 mg. of hydrochlorothiazide given orally produced a gradual reduction in urinary output, the maximum effect taking place in approximately one month. Electrolyte-loading tests 'indicated that electrolyte alterations were not responsible for this action' and 'it is postulated that at the distal renal tubules, thiazides compete with or substitute for antidiuretic hormone'. On the eighth day of treatment the dosage of hydrochlorothiazide was reduced to 100 mg. a day, and five months later the patient was adequately controlled on this dosage together with a daily dose of 40 mEq. of potassium.

The use of aminopyrine in a 43-year-old man who 'manifested the uncommon combination of diabetes insipidus and diabetes mellitus' is reported by T. Balsam and H. M. Katzi (*Ibid.*, p. 1112). On admission he had obvious symptoms of diabetes mellitus which responded well to routine treatment, but polyuria was still sufficiently marked to warrant further investigation which confirmed that he was also suffering from diabetes insipidus. Oral administration of 0.6 g. of aminopyrine thrice daily produced a

'decided decrease' in thirst and a marked drop in daily fluid intake. Seven months later the improvement was still maintained but if the patient forgot to take his tablets symptoms recurred. The maintenance dose was 0.6 g. thrice daily for two days followed by one day free of medication 'to prevent resistance to the drug's effectiveness'. It is concluded that 'the water and salt retaining properties of this drug make it a valuable adjunct in therapy of diabetes insipidus in patients who will not or cannot take vasopressin tannate'. Whilst 'its potential hæmatological hazard has been greatly overemphasized', close observation should be exercised and 'it would appear prudent to caution the patient against concomitant use of barbiturates'.

External Cardiac Massage in Children

ATTENTION is drawn by W. B. McKelvie and P. McKelvie (*British Journal of Anæsthesia*, July 1961, **33**, 371) to the value of external cardiac massage as a means of resuscitation of young children. Details are given of three cases (aged 4½, 3½, and 5 years, respectively) in which the children were successfully resuscitated after cardiac arrest. In two, external cardiac massage alone was successful; in the third this had to be supplemented by trans-abdominal (open) massage. The method is as follows. 'The operator stands on the right side of the patient; the flat of both hands is placed low down on the left side of the thorax, to cover some of the area over the sternum and floating ribs; very firm pressure followed by relaxation is applied at about the normal pulse rate. Adequate pressure may be applied with the patient supine on the Sorbo-covered operating table. In the case of a very small child, it is advantageous to place one hand behind the left side of the chest and the other in front to effect compression. The procedure may be carried out by the anæsthetist during the short time in which the surgeon is preparing to open the chest for direct cardiac massage'. It is suggested that should a heart beat not be felt after twenty to thirty 'strokes', internal direct cardiac massage should be carried out at once.

Bronchiectasis in Childhood

A REVIEW of the course of bronchiectasis in childhood has been made by Mary E. Avery and her colleagues (*Bulletin of the Johns Hopkins Hospital*, July 1961, **109**, 20), based upon the records of 66 children who were under the age of 14 years at the time of onset of chest symptoms. Proven bronchiectasis was not found in siblings. Members of the patients' families had undiagnosed chronic lung disease in five instances, tuberculosis in twelve, and asthma in seven. The incidence of prematurity was not significant. The onset of symptoms occurred before the age of 5 years in 74%, and in the first year of life in 35%. The usual onset was with an acute febrile illness, diagnosed as pneumonia in 22, pertussis in 10, tuberculosis in seven and measles in four. In 12 the onset was insidious with a chronic cough. The most severe disease was noted in those patients whose symptoms began before the age of 3 years. In all four children who died the onset was between the ages of 1 and 3 years. The effect of bronchiectasis on linear growth was not striking. Of the 13 children with some effect upon linear growth, seven had bilateral disease, but it is noted that 14 of the 53 children in whom growth was not affected also had bilateral disease. The only two with severe growth retardation had asthma. At least 45% of the children had radiological and clinical evidence of sinusitis. The presence of sinusitis did not appear to influence the prognosis of the bronchiectasis. On the other hand, three times as many patients with sinusitis had a persistent chronic cough as compared with those without sinusitis. 'Definite indications' for surgery are said to be 'irreversible bronchial obstruction or the presence of localized infections which cannot be controlled by antibiotics', but 'there is seldom reason for haste in recommending resection in patients with bronchiectasis'.

Phenacetin Nephritis

'ANY heavy phenacetin consumer who develops progressive impairment of renal function is likely to have chronic interstitial nephritis, especially if there is little to find in the urine and no history of previous renal illness', according to J. G. Buchanan (*New Zealand Medical Journal*, May 1961, **60**, 207) in reporting a fatal case of 'phenacetin-induced chronic interstitial nephritis'. The patient was a 50-year-old man who for at least two years had taken 15 tablets daily of a proprietary tablet containing 3 grains (0.2 g.) of phenacetin in combination with aspirin and caffeine. For two months before admission to hospital he had complained of headache, became increasingly drowsy and 'appeared to be cyanosed'. On admission to hospital he was uræmic and the blood contained 15% sulphæmoglobin. 'Despite energetic treatment of his uræmia, his condition gradually deteriorated and he died in a coma sixteen days after admission'. The diagnosis of chronic interstitial nephritis was confirmed at necropsy. The amount of phenacetin necessary to cause renal damage is variable but 1 gramme or more

daily is 'certainly dangerous'. Attention is drawn to the fact that 'the two symptoms most likely to lead to prolonged self-administration of phenacetin are chronic headache and various musculo-skeletal pains'. As persistent headache is a common symptom of chronic renal disease, the dangers of a vicious circle being established are obvious.

Chylous Ascites

In an analysis of 15 cases of chylous, or 'milky', ascites seen at a New York Hospital, M. L. Kelley, Jr., and V. W. Logan (*New York State Journal of Medicine*, July 1, 1961, **61**, 2307) report that the 'underlying disease processes, responsible for the milky peritoneal effusions' were abdominal malignant conditions in six patients, cirrhosis of the liver in three, malignant lymphomas in two, advanced renal disease in two, widespread tuberculosis with secondary hepatic amyloidosis in one, and congenital lymphatic dysplasia in one. Although 'spontaneous milky peritoneal effusions are usually the result of extrinsic or intrinsic lymphatic obstruction', there remain to be explained the 'large number of patients with extensive abdominal or retroperitoneal malignant conditions' who 'form ascitic fluid which is clear rather than milky even in the face of what is undoubtedly a considerable lymphatic block'. It is suggested that the explanation for this is 'the rapidity with which collateral lymphatic channels are formed'. Pleural effusion occurred in seven of the 15 patients in this series, and in six of these it was milky. The total lipid content of the ascitic fluid ranged from 320 to 940 mg. per 100 ml. Attention is drawn to the fact that in two of the patients with cirrhosis 'a medical regimen of salt restriction, diuretics, high-calorie diet, vitamins and avoidance of alcohol' alleviated completely the formation of milky fluid'.

Seromucoid in the Diagnosis of Cancer and of Jaundice

As a result of their studies in two series of patients, E. Cameron and his colleagues (*Scottish Medical Journal*, July 1961, **6**, 301, 308) consider that seromucoid (SM) estimations can provide valuable assistance in the diagnosis and management of cancer and also in the diagnosis of jaundice. In a series of 1000 patients there were 206 in whom cancer was suspected on clinical grounds and about 90% of these (180) had raised SM levels at the time of their first hospital attendance. Although the remaining 10% had normal values, 'in practice this failure rate is not serious, since the majority of such patients had small tumours which had attracted early attention because of their superficial situation'. Raised SM levels were obtained in a number of patients with non-malignant disease but 'the majority of non-malignant diseases associated with high SM levels are easily recognized and do not commonly enter into the differential diagnosis of cancer'. The test was found particularly useful in the detection of intra-abdominal cancer: 'Its routine application to elderly patients presenting with such complaints as anæmia, bowel irregularity, jaundice, hæmatemesis, melæna, hæmaturia and prostatism has often revealed clinically unsuspected malignancy'. Amongst other uses the test is also of value in assessing response to treatment, 'as a prognostic index at follow-up examination', and is particularly useful in adjusting œstrogen dosage in the management of prostatic cancer. It is concluded that 'any test for cancer carrying a 90% precision is worth adopting as a routine procedure'.

In another series, SM levels were estimated in 73 patients with jaundice, and proved a 'valuable method of distinguishing hepatocellular from obstructive jaundice', the levels being below normal in the former and significantly higher in the latter. In addition the SM level can often indicate whether the obstruction is due to stone or tumour. The recommendation is therefore made that seromucoid estimation should be added to 'the standard profile' of liver-function tests.

'Nidoxital' in Radiation Sickness

A clinical trial of 'nidoxital', a preparation containing a combination of drugs that exert both central and peripheral actions is reported by R. Finney (*Clinical Radiology*, July 1961, **12**, 229). Each capsule of 'nidoxital' contains pyridoxine hydrochloride 50 mg., pentobarbitone sodium 15 mg., benzocaine 100 mg., and nicotinamide 25 mg., and the recommended dosage is 1 capsule taken half-an-hour before meals, up to a maximum of ten during the day. Fifty-one patients who received standard x-ray treatment after mastectomy for carcinoma of the breast took part in a clinical trial, each having 'nidoxital', pyridoxine, or placebo capsules according to randomized selection. Concluding that ' "nidoxital" reduces all symptoms arising from irradiation exposure by a significant degree as compared with pyridoxine', the author notes that two-thirds of the patients taking this preparation remained asymptomatic throughout the trial compared with one-third of the controls. This result is statistically significant at the 10% level. Nausea, headache and malaise were the most difficult symptoms to control, whilst anorexia appeared to be the easiest to abolish. No side-effects were noted.

REVIEWS OF BOOKS

Cerebral Palsy in Childhood and Adolescence. Edited by PROFESSOR J. L. HENDERSON, M.D., F.R.C.P.ED. Edinburgh: E. & S. Livingstone Ltd., 1961. Pp. 403. Illustrated. Price 35*s.*

THIS attractive volume shows what can be done by imaginative planning of the resources of a Scottish university and associated hospital region, with a population of 410,000, to provide the basis of a comprehensive survey from birth up to 21 years. Problems of diagnosis and classification are carefully set out and tabulated, and compared with the results of surveys elsewhere.

The Dundee team represents adequately the fields of pædiatrics, educational psychology, public health, orthopædic surgery, the special senses and orthodontics. The orthopædic chapter is very detailed, but does not give the prominence to hip dislocation which experience elsewhere would suggest. The lengthy ophthalmological chapter is full of suggestive interest. Throughout the book the data under discussion are set out clearly in numerous tables. The psychological study emphasizes the problem of the associated mental handicap of a large proportion of children with cerebral palsy. The emotional and social factors affecting the progress of these children, and their prospects of later employment are set out with sympathy.

The closing chapters bring into focus considerations of etiology and recommendations for planning the care of patients with these handicaps. All doctors who work with children will find their thinking stimulated by reading this book.

Intra-Abdominal Crises. By K. D. KEELE, M.D., F.R.C.P., and N. M. MATHESON, M.R.C.P., F.R.C.S., F.A.C.S. London: Butterworth & Co. (Publishers) Ltd., 1961. Pp. 397. Illustrated. Price 50*s.*

THERE are several excellent books by surgeons on surgical abdominal emergencies but there are few which deal with abdominal crises largely from the physician's standpoint, as this one does. It is a wholly admirable survey of the subject. Written jointly by a physician and a surgeon, it bears the unmistakable stamp of the personal experience of the authors. The subject is not an easy one and no attempt is made to minimize the diagnostic difficulties or to oversimplify. Although modern methods of investigation, both radiological and chemical, are fully discussed the emphasis throughout is on the clinical approach. Moreover, the patient and his symptoms are seen in perspective and the part played by the general practitioner, the casualty officer and the resident doctors is stressed.

It may perhaps be felt that some exceedingly rare conditions receive too much space but this is a small criticism and the general level of the content is excellent. This is not a book for the undergraduate but there will be few doctors engaged in general medicine or general surgery who will not feel stimulated and fortified by reading it.

The Medical Management of Acute Poisoning. By GORDON CUMMING, B.SC., PH.D., M.B., CH.B., A.R.I.C. London: Cassell & Co. Ltd., 1961. Pp. 128. Illustrated. Price 10*s.* 6*d.*

THIS is a short, inexpensive and practical handbook, which also includes a chapter on the psychiatric aspects of poisoning by Dr. Myre Sim. After dealing with the general principles of treatment, respiratory, circulatory and renal failure, the main emphasis is on poisoning by carbon monoxide, barbiturates, salicylates and alcohol which are those most commonly observed. It is interesting to note that the author stresses that in the majority of cases of ingested poisons gastric lavage should be limited in amount to one litre. An adequate amount of statistical, scientific and physiological information is included. In fact, a great deal of most valuable knowledge essential to the casualty officer, hospital resident and general practitioner is contained in a small compass and any doctor likely to be faced with the problems of poisoning would be well advised to possess a copy of this book.

Clinical Disturbances of Renal Function. By A. G. WHITE, M.D., F.A.C.P. Philadelphia and London: W. B. Saunders Co., 1961. Pp. 468. Illustrated. Price 73*s.* 6*d.*

THIS book is intended to guide the physician in the practical approach to the clinical problems associated with renal dysfunction. It consists basically of an introductory chapter dealing with the theoretical background of renal function, fifteen chapters dealing with clinical problems, and three appendixes. The book is well produced and the illustrations are numerous and in the main lucid. Unfortunately the introductory chapter is difficult to understand and some of the illustrations confuse rather than clarify the issue. It is suggested that the prospective purchaser study the excellence of the

clinical chapters rather than concentrate too much on the introduction. The chapters dealing with clinical problems are fascinating and instructive, the ideas expressed seem sound and practical. It is interesting to note the attention given to excessive ADH activity in the pathogenesis of nephrotic œdema, a view which has been expressed in this country previously.The book contains many valuable references to the American literature and one can only regret that so little attention is paid to world literature since a proper spectrum of opinion would thereby have been included.

This book should prove of great value to the hospital physician with laboratory backing and of great interest to any practitioner interested in the problems of renal disease and the pathological physiology of renal dysfunction. The appendixes dealing with renal anatomy, renal transport mechanisms and pharmacological mechanisms underlying the action of diuretic agents are particularly interesting. The chapter on clinical methods of the evaluation of renal dysfunction is lucid and instructive.

Virus Meningo-Encephalitis. Ciba Foundation Study Group No. 7. Edited by G. E. W. WOLSTENHOLME, O.B.E., M.B., M.R.C.P., and MARGARET P. CAMERON. London: J. & A. Churchill Ltd., 1961. Pp. 120. Illustrated. Price 12*s.* 6*d.*

THIS volume records the proceedings of a study group on virus meningo-encephalitis which met last September at the Ciba Foundation in honour of Professor K. Todorovic, Rector of the Medical Faculty at Belgrade and a leader in the study of infectious disease. It is an admirable record of an informal yet informative meeting of experts from many different countries which shows full well the value of such discussions between specialists in different fields, clinicians, virologists, epidemiologists and pathologists.

The first part deals mainly with the virological aspects. A general survey by Professor Todorovic is followed by a chapter on the main viral causes by A. D. Macrae, two on ECHO viruses and others on various aspects of coxsackie and poliovirus infections. Living in this country we tend to forget the important role of insects in communicable disease and three papers on arthropod-borne encephalitis from Finland and Czechoslovakia show what a real problem these diseases are. A fascinating account by W. F. Scherer from Minnesota on an epidemiological survey of encephalitis in Japan shows how some of the problems of control are being tackled. This small volume contains many other interesting articles on the significance of inclusion bodies, on symptomatology and on post-infectious encephalitis as well as an excellent account of the discussions that took place. It is extremely well produced and gives a good insight into this important problem as well as being a pleasant reminder of a most enjoyable meeting.

Light Coagulation. By GERD MEYER-SCHWICKERATH, M.D. Translated from the German by STEPHEN M. DRANCE, M.B., F.R.C.S. London: Henry Kimpton; St. Louis: C.V. Mosby Co., 1960. Pp. 114. Illustrated. Price 71*s.* 6*d.*

ONE of the most dramatic developments of post-war ophthalmology has been the novel method of treatment of some retinal conditions without open surgery, by trans-pupillary phototherapy. For many centuries it has been known that eclipses, and particularly that of 1912, are followed by permanent retinal damage in those who unwisely look into the sun without adequate protection. The optical system of the eye acts like a magnifying glass focusing on the macula the rays of sunlight which are degraded to heat by the retinal pigment epithelium. With great originality and ingenuity Professor Meyer-Schwickerath has applied this phenomenon to therapeutic ends, employing a xenon tube to produce rays comparable in intensity and quality to those of the sun. By means of his apparatus, which has been developed by Carl Zeiss, it is possible to produce controlled burns resembling those of transcleral diathermy and to cause adhesions between retina and choroid so preventing, and in some instances curing, the retinal tears which produce detachments. It is also possible to destroy tumours such as retinal angiomas by this method though as yet it is doubtful whether malignant tumours of the choroid are amenable. In addition, a hole can be burnt in the iris with this apparatus, so destroying a tumour or producing an optical iridectomy without opening the eyeball.

Professor Meyer-Schwickerath's book is a masterly exposition of this new therapeutic weapon and an indispensable guide to everyone who wishes to make full use of its capabilities. Obviously it is a book for the specialist but its fascinating story would make interesting reading for any medical man.

The Management of Pædiatric Practice. By HUGH C. THOMPSON, M.D., and JOSEPH B. SEAGLE, M.D., M.S. Springfield, Illinois: Charles C Thomas; Oxford: Blackwell Scientific Publications Ltd., 1961. Pp. 172. Illustrated. Price 60*s.*

THIS is an interesting and readable book which is intended for the practising American pædia-

trician but is also of interest to British pædiatricians, both for its descriptions of child management and as an account of the work of their American counterparts. It is apparent that the authors have a wide knowledge of child behaviour and parent management and the description of the physician's art in handling children is masterly and born of infinite patience and experience. The methods to be adopted in order to build up a successful private practice are well described, and for the American pædiatrician obviously necessary. To a British pædiatrician this part of the book reads almost like a documentary on the American way of life and the reviewer believes that after reading this book most pædiatricians in this country, in common with himself, would be thankful that they practise on this side of the Atlantic and are relieved of the financial approach to their work. How strange to our ears is the sentence: 'The greater profit to the physician from giving injections, rather than writing prescriptions, should not be allowed to influence his decision'.

For those in Britain who have not had the opportunity of seeing American pædiatric practice at first hand this book is especially valuable in assisting them to visualize the scene, and it should certainly be read by any pædiatrician who contemplates emigrating to the United States. The difference between the British consultant pædiatrician and the American family pædiatrician comes home forcibly in the reference to emergencies which are described as being 'very rare in pædiatrics'. This book most certainly achieves its aims and as a most readable description of American pædiatricians at work it can be thoroughly recommended.

Handicapped Children. By JOHN D. KERSHAW, M.D., D.P.H. London: William Heinemann (Medical Books) Ltd., 1961. Pp. 228. Price 21*s.*

THIS is a good guinea's worth. Written mainly for social workers and teachers it is nevertheless full of valuable information for family practitioners, pædiatricians and other specialists concerned with the handicapped child. Dr. Kershaw's experience at the United Nations has given him a broad outlook and although what he has to say is particularly applicable to the United Kingdom he approaches each aspect of the problem with a kindly and unlimited regard for what the handicap means to the child and his parents. After a preface and a chapter called 'The problem in outline' he gives six valuable sections on general aspects before tackling the individual handicaps. There is an appendix on handicapped children in less-developed countries and another on the legal aspects of handicap in childhood.

The Association of American Physicians. Its First Seventy-Five Years. By J. H. MEANS, M.D. London: McGraw-Hill Ltd., 1961. Pp. 316. Price 77*s.* 6*d.*

ALTHOUGH primarily of domestic interest, this intriguing labour of love has a much wider interest. As a history of American medicine during the last seventy-five years—from a somewhat unusual angle—it will appeal to many readers outside the United States. All the great names of American medicine—from Osler and Welch down to Hench and Thorne—appear here, whilst the outlines of the papers read at the annual meetings of the Association are a fascinating guide to trends (and fashions) in medicine throughout the years.

Parts, of course, are of little more than passing interest to the outsider, but Dr. Means' pen-sketches of the leading members of the Association are a joy to read, and from his own recollections, as well as those of other members of the Association, he has been able to throw a fresh light on some of the great men of the era. Typical of the delightful style in which the book is written is the account of what happened on the occasion in 1936 when Lord Horder attended the annual meeting of the Association. Riesman had read a paper on splenectomy in subacute bacterial endocarditis. In the subsequent discussion 'Lord Horder, a peppery little man, leaped to his feet and disagreed violently with everything Riesman had said, which, of course, was his privilege. A couple of members came to Riesman's defence, and Riesman himself accepted the criticism in very good spirit. He did permit himself to say that if Horder knew a treatment that gave as good palliation as he had seen with splenectomy, he would like to hear about it; no further remark by Horder'.

This is a book which the discriminating reader will browse through with profit and pleasure.

NEW EDITIONS

Textbook of Medical Treatment, edited by Sir Derrick Dunlop, M.D., F.R.C.P., F.R.C.P.ED., Sir Stanley Davidson, M.D., F.R.C.P., F.R.C.P.ED., and S. Alstead, C.B.E., M.D., F.R.C.P., F.R.C.P.ED., F.R.F.P.S., in its eighth edition (E. & S. Livingstone Ltd., 60*s.*), is as good as ever and this is saying a lot. Eight editions and seven reprints within twenty-two years are ample evidence of its popularity—and the reason for its popularity is not far to seek. It is written by clinicians and carefully edited so that the emphasis throughout is on what the man in practice requires. Unlike so many other books on the subject it is not out of date before it is published, because it does not claim to discuss the latest therapeutic

craze. Its aim is to provide the clinician—whether consultant or general practitioner—with a sound, reliable and up-to-date account of methods of treatment which have proved of value—whether they were introduced yesterday or today.

Clinical Endocrinology, by Laurence Martin, M.D., F.R.C.P., third edition (J. & A. Churchill Ltd., 28*s*.).—Although Dr. Martin has lost the valuable aid of Dr. Hynes, his notable sense of balance and industry has ensured that the admirers of the first two editions of this book shall not be disappointed by the third. Far from it. The practical management of those endocrine disorders which are most commonly encountered is brought right up to date. Notable are the discussions of the place of radioactive iodine in the diagnosis and treatment of thyroid disease, and of endocrine treatment in menstrual disorders—this with the help of Mr. Bruce Eton. The new chapter on 'Human sexual development' deals skilfully with a rapid advance in a fascinating and clinically important field. All this makes the book well worth the increase in price.

Roxburgh's Common Skin Disorders, revised by Peter Borrie, M.D., F.R.C.P., in its twelfth edition (H. K. Lewis & Co. Ltd., 50*s*.) shows every sign of careful revision. It has given Dr. Borrie the opportunity of recasting the design of the book. This he has done so effectively that he has been able to bring it right up to date and impress upon it his own personality without in the least detracting from the characteristics which marked the book when it was first planned and written by Dr. Roxburgh and which made it the outstanding practical textbook on the subject. To take over the responsibility for someone else's book is always a difficult task; to make a success of the transition is a feat which few achieve. Dr. Borrie's success in this respect is indeed noteworthy, and he can rest assured that what is now his book remains one of the best books on the subject for the general practitioner and the senior medical student.

Symptoms and Signs in Clinical Medicine, by E. Noble Chamberlain, M.D., M.Sc., F.R.C.P., in its seventh edition (John Wright & Sons Ltd., 45*s*.) is deservedly popular with students starting clinical medicine. It is not concerned with biochemistry or electroencephalography but with the art of taking a history, examining a patient and coming to a diagnosis without using the newer methods of investigation. The author rightly points out in the preface to this new edition that these new methods may be dangerous. Wisdom is needed in deciding when they should be used. The text has been revised and many excellent new illustrations have been added. 'The foundations of our art' is a new chapter introduced in this edition. Those who are so anxious today about the overburdening of the medical student can be reassured that this thumb-nail sketch of the history of medicine can be digested with ease.

Principles of Medical Statistics, by Sir Austin Bradford Hill, C.B.E., D.Sc., PH.D., F.R.S., in its seventh edition (The Lancet Ltd., 12*s*. 6*d*.) has undergone a thorough overhaul which ensures that it remains firmly established as the best guide to the subject for medical students and practitioners. It may not be as 'elementary' as the first edition, but it is a sign of the times that the quarter of a century which has almost passed since this little classic first saw the light of day has witnessed a complete incorporation of statistics into the philosophy and practice of medicine. Such a whole-hearted incorporation is not without its dangers, but the author of these 'Principles' is the first to recognize these and to warn the enthusiast of the pitfalls awaiting him if he treads unwarily in this field.

Forensic Medicine, by Keith Simpson, M.D., in its fourth edition (Edward Arnold (Publishers) Ltd., 32*s*. 6*d*.) is an admirable example of how to condense the essentials of a subject into relatively small space without any loss of accuracy or degradation of style. This is not a book for the expert, but there is none better for the medical student or the general practitioner. Neither will go very far wrong if he keeps this book beside him, consults it when necessary and imbibes its teaching. So far as students are concerned, it will prove invaluable in those many medical schools throughout the country which are renowned for their persistent refusal to provide adequate instruction in forensic medicine.

Gynæcology for Senior Students of Nursing, by John Cairney, C.M.G., D.Sc., M.D., F.R.A.C.S., in its second edition (N. M. Peryer Ltd., 30*s*.), is a good book for those to whom it is directed. It is comprehensive and includes useful sections on psychology, contraception and pre- and post-operative management. The line drawings are first-class.

The contents of the November issue, which will contain a symposium on 'Dental and Oral Disease', will be found on page A 154 at the end of the advertisement section.

Notes and Preparations see page 593.
Notes from the Continent see page 597.
Fifty Years Ago see page 599.
World Health News see page A 17.
Motoring Notes see page A 101.
Travel Notes see page A 105.
Bridge Notes see page A 109.
From a Sussex Window see page A 111.
Official and Proprietary Names see page A 115.
Approved Names see page A 119.

NOTES AND PREPARATIONS

NEW PREPARATIONS

'DUPHASTON' tablets each contain 5 mg. of 6-dehydro-retro-progesterone (isopregnenone), which is said to be a highly potent orally active progestational agent 'devoid of androgenic, renotropic, anti-inflammatory and glycocorticoid properties'. Indications for their use include dysmenorrhœa, primary and secondary amenorrhœa, the postponement of menstruation, and threatened and habitual abortion. Available in tubes of 20 and bottles of 100. (Crookes Laboratories Ltd., Park Royal, London, N.W.10.)

'IFONUTROL' is a sterile fat emulsion for intravenous use containing 15 w/v% cottonseed oil and 4 w/v% dextrose. It provides 1,600 calories per litre and is indicated for patients who are unable to ingest adequate food orally, 'especially if this inability is likely to be of long duration'. It is claimed that the incidence of side-effects previously associated with intravenous administration of fat emulsions has been 'markedly reduced' by purifying the vegetable oil and phosphatide components. Available for hospital use in 500-ml. transfusion bottles, each with a disposable giving set, in cartons of 6. (Astra-Hewlett Ltd., King George's Avenue, Watford, Herts.)

'VASCARDIN' tablets each contain 10 mg. of sorbide nitrate which is a new coronary vasodilator said to have a 'dramatic' effect in reducing, or eliminating, the frequency and severity of anginal attacks. Its action is described as equivalent to that of glyceryl trinitrate in therapeutic effect and rapidity of onset 'but with the great advantage of giving prolonged control of angina pectoris for up to six hours'. Available in containers of 100 tablets. (Nicholas Laboratories Ltd., 225 Bath Road, Slough, Bucks.)

PHARMACEUTICAL NOTES

BURROUGHS WELLCOME & CO. announce that their dipipanone-cyclizine preparation, 'pipadone compound', has now been withdrawn and has been replaced by 'diconal' tablets. These contain a smaller dosage of dipipanone hydrochloride (10 mg. instead of 25 mg.) and of cyclizine hydrochloride (30 mg. instead of 50 mg.). Available as red scored tablets in containers of 25 and 100. (The Wellcome Building, Euston Road, London, N.W.1.)

PFIZER LTD. announce that 'dulcolax' suppositories are now available in a half-size especially formulated for children up to the age of ten years. Available in boxes of 6. (Boehringer Ingelheim Division, Sandwich, Kent.)

SMITH KLINE & FRENCH LABORATORIES LTD. announce that as from September 1, 'furadantin' (nitrofurantoin) tablets will be pentagonal in shape. The tablet strength and colour will be unchanged. (Welwyn Garden City, Herts.)

OFFICIAL NAMES OF DRUGS

ON page A 115 readers will find a list of some of the newer and less familiar drugs which are mentioned by their official names in the articles in this issue, together with their equivalent proprietary names.

On page A 119 there is a list of the 'Approved Names' which have been issued by the British Pharmacopœia Commission since October 1960.

NEW APPARATUS

Robophone is the name of the latest automatic machine which will answer the telephone, broadcast a pre-recorded announcement giving the subscriber's expected time of return, and accept messages of any duration; it can also be used for dictation. Available on a contract-hire basis for periods of 3, 5 or 7 years at rates from 27*s.* a week. Installation and maintenance are free. (Robophone Ltd., Shropshire House, Tottenham Court Road, London, W.1.)

FILM NEWS

Profound Hypothermia (16 mm., colour, sound, running time 33 minutes) shows the repair of a ventricular septal defect in a seven-year-old child, by the new technique for open heart surgery which was developed in the department of experimental surgery at Westminster Hospital and which does not require an artificial oxygenator or a system of cardiac suction. Produced by Verity Films in association with the Film Producers' Guild Ltd., with the cooperation of the Thoracic Unit of Westminster Hospital and the A.P.V. Co. Ltd., and available for showing to members of the medical profession upon application to Department A., Allen & Hanburys Ltd., Bethnal Green, London, E.2.

FORTHCOMING CONFERENCE

The Training of the Family Doctor for his Work in the Community will be the subject of a symposium organized by the College of General

Practitioners and sponsored by the Wellcome Foundation, to be held on Sunday, November 26, 1961, at the Wellcome Building, Euston Road, London, N.W.1. Application should be made to the Secretary of the College at 41 Cadogan Gardens, London, S.W.3.

ROYAL SOCIETY OF MEDICINE

THE next meeting of the Section of General Practice will be held at 8.15 p.m. on Wednesday, October 18, when Dr. L. W. Batten will give the valedictory address, entitled 'Quo Vadimus'.

MARJORY WARREN MEMORIAL FUND

THE British Geriatrics Society has initiated and is supporting a fund to commemorate the pioneer work of the late Dr. Marjory Warren, consultant physician in geriatrics at the West Middlesex Hospital, Isleworth, who was killed in a car accident in September 1960. The object of the fund will be to finance scholarships, tenable in this country or abroad, to promote the study of the medical, nursing or social aspects of care and treatment of the elderly. Donations should be sent to: Barclays Bank Ltd., 54 Highgate High Street, London, N.6.

THE KING'S FUND

THE annual report of the King Edward's Hospital Fund for London for 1960 shows that the capital resources of the Fund now total some £9.5 million, with an annual income of around £485,000. In addition, in 1960, the income from legacies totalled £153,385. The total expenditure of the Fund was £584,249, over £300,000 of which went in grants to hospitals. One of the more interesting of these grants is that of £37,700 to the Kingston upon Thames Hospital for the construction of a doctors' centre in the grounds of the hospital. According to the report, 'this will be in the nature of a club providing meals for all doctors on the staff of the hospital, general practitioners, medical officers of health, factory doctors, or any others practising in the district. There will be a lecture room and library, and it is hoped that the centre will provide a meeting place where friendships will be made and problems can be discussed on an informal basis'.

THE NUFFIELD FOUNDATION

THE sixteenth report of the Nuffield Foundation shows that the allocations in the year 1960-61 have passed the 'notable landmark' of £2 million. Fifteen different countries and territories of the Commonwealth have received grants amounting to £385,000. Typical of the overseas work supported by the Foundation is an investigation into the important problem of the effects of malaria on African vital statistics for which a grant of £29,000 over a five-year period has been made to the East African Institute of Malaria and Vector Borne Diseases in Tanganyika. At home £250,000 has been set aside for the development of industrial health schemes, whilst nearly the same sum, £220,000, has been allocated to meet the capital cost of building and equipping what is to be known as the Nuffield Institute of Nuclear Medicine at the Middlesex Hospital Medical School, where the increasingly complex problems of radioactivity as applied to medicine can be more effectively studied. Working jointly with the Joseph Rowntree Memorial Trust the Foundation is setting up, and endowing for ten years, a National Institute for Social Work Training which will come into being at the Mary Ward Settlement on October 1 this year.

CARE OF THE ELDERLY

IT is now twenty-one years since the National Old People's Welfare Council was established to coordinate the help of the voluntary and statutory bodies concerned with the care of the elderly. Considerable progress has been made since then but, as emphasized in the Council's recently published annual report, much remains to be done 'if older people who require help are to be cared for as they have the right to expect and as the rest of the community would wish them to be'. The problems involved are increased by the fact that there are now two million more people of pensionable age (7½ million) than when the council was set up in 1940. The wide scope of the council's activities includes cooperation with countries overseas, and during the year plans of homes were sent to Israel, a prototype plan for a club was sent to Australia, and requests for advice or publications were received from all parts of the world.

MODERN VENEREOLOGY

IN drawing attention to a marked increase in early contagious cases of syphilis in Edinburgh in 1960, Dr. Robert Lees, the physician-in-charge of the department of venereal disease, comments as follows in the annual report of the medical officer of health for that year: 'Two sources account for the greater part of this increase, the first being a soldier who infected a woman in Fife, and she in turn led to the infection of five individuals. The second source was a group of male homosexuals; the infection was probably introduced to Edinburgh by a man who came from London and spent some weeks here. It is probable that we did not trace several contacts as homosexuals are very secretive on this subject. One man, a University graduate, had at least three consorts in different parts of the country and he stated that he would warn them to undergo medical examina-

tion, but we have no evidence that they complied. One prostitute, whose name and description is known, came to the Edinburgh area from the Southampton area. She was responsible, we think, for three infections while in Edinburgh, and a colleague states that she is suspected of nine infections in the South of England. But so far she has not been traced, examined or treated'.

AMERICAN OBSTETRICS

ACCORDING to a report in *A.M.A. News*, 'a physician, who told an expectant mother that he would not deliver the child at the mother's home and insisted that she come to a hospital, was held not liable in the child's death when the mother did not follow his advice. A Louisiana Appellate Court said that evidence showed that "no physician in the area any longer undertakes childbirth in the patient's home, but all require, even (and especially) in emergency conditions, that the expectant mother be brought to hospital". The mother had called in an aged midwife. When the midwife saw the delivery would be difficult, she advised securing a doctor. Telephone calls to three M.D.s brought advice from each that the mother be taken to a hospital. When she was brought to the hospital six hours later, the unborn child was already dead'.

GEOPHAGY AND INTESTINAL OBSTRUCTION

EARTH-eating, sometimes called geophagy, is common in Africa where certain tribes entertain the notion that the habit promotes fertility, so that mothers give it to their children. The results of this practice may be unfortunate, including as they do 'intestinal polyparasitism' and nutritional deprivation. An unusual complication of this habit is reported by D. R. W. Haddock (*E. Afr. med. J.*, 1961, **38**, 314) in the case of a five-year-old African girl in whom a diagnosis of obstructed umbilical hernia was made. At operation the foreign body removed from the bowel was found to be 'a cylinder of closely compacted reddish earth with a few small stones', about $\frac{7}{8}$ inch (22 mm.) in diameter and one inch (25 mm.) long. The child, who appeared mentally normal, admitted eating earth, but only on one occasion and for no given reason.

BLOODY TEARS

DETAILS are given by P. G. Belau and C. Wilbur Rucker (*Proc. Mayo Clin.*, 1961, **36**, 234) of what is claimed to be the first case to be reported of 'bloody tears due to the pubic louse'. The patient, a 2-year-old boy, with a history of 'blood in his tears' for three months, was 'an alert healthy child' and the only abnormality on physical examination was the presence of a dark powdery material on the lower eyelids. He was made to cry and the tears from the left eye were reddish brown and stained the cheek: examination of these revealed the presence of hæmoglobin but no red blood cells. On a return visit the mother produced a small insect she had seen crawling on the child's eyelashes and this proved to be *Phthirus pubis*. Examination of the eyes then disclosed the presence of numerous nits but there was no infestation of the eyebrows or scalp. Following removal of the nits and the local application of yellow oxide of mercury ointment there has been no recurrence of blood in the tears.

It is noted that in an American report of five cases of phthiriasis palpebrarum in children all but one were doctors' children.

ANTITUSSIVE LIQUORICE

FRESH evidence that the traditional use of liquorice in cough mixtures has more justification than the pharmacologists have been prepared to admit of late is now forthcoming. According to D. M. Anderson and W. G. Smith (*J. Pharm. Pharmacol.*, 1961, **13**, 396), derivatives of glycyrrhetinic acid have a central antitussive effect. Several derivatives had approximately the same potency as codeine when given subcutaneously to guinea-pigs, and one of them exhibited the same degree of activity after oral administration. The authors comment that if this orally active preparation 'has activity of this magnitude in man, the traditional use of liquorice for cough therapy can be considered to have some rational basis'.

COGNAC FOR TONSILLITIS

IN 'A Note on the Medical Use of Sugar and Chocolate Capsules Containing Cognac or a Liqueur', F. Parkes Weber ('Miscellaneous Notes' [Twelfth Series]) writes: 'When one of these is allowed to dissolve in the mouth, the part about one's tonsils becomes flooded with alcohol, and this is the simplest and the best method of applying alcohol to the region. I think it constitutes a valuable method in opposing the development of acute streptococcal sore throat (*Angina Faucium*)'.

'BIRTH ATTENDANTS'

'To give reassurance and the comfort of companionship to women in labour, two of the hospitals under the Pontypridd and Rhondda H.M.C. are to make available retired midwives, specially chosen for sympathetic personality, to sit by the patients. They will not have any midwifery duties, but will simply perform for the mothers this service that, in busy short-staffed

maternity departments, cannot be given by the nursing staff'.—*Nursing Times*, 1961, **57**, 888.

SUNLIGHT AND BEER

It is practically a century since it was first reported that beer develops an unpleasant flavour on exposure to sun. No explanation of this phenomenon has hitherto been forthcoming. According to Y. Obata and his colleagues (*Nature* (*Lond.*), 1961, **190**, 635), however, it is associated with the humulones and lupulones in hops. By a photochemical reaction between the 3-methyl-2-butenyl group in the molecules of humulones or lupulones and certain sulphur-containing compounds present in beer, 3-methyl-2-butenyl mercaptan is produced and it is this mercaptan derivation which is responsible for the so-called sunlight flavour of beer.

PUBLICATIONS

Circulatory Ulcers: A Physical Approach, by Hilton G. Tranchell, B.D., M.C.S.P., and Charles R. Bannister, M.C.S.P., is concerned with the treatment of ulcers of the leg from the standpoint of the physiotherapist. The wide range of treatment available in the physiotherapy department is fully described and the authors' results indicate their enthusiasm. Their description of the etiology and pathology of ulceration of the legs, however, is unsatisfactory. The basic fault in most ulcerated legs is a failure of the calf-muscle pump and this is not clearly brought out in the book. Once it is realized that properly applied elastic support can heal most ulcers, it can be appreciated that the other physical methods that are available are useful but to a very limited extent. (John Wright & Sons Ltd., price 12*s.* 6*d.*)

Britain's Search for Health, by Paul F. Gemmill, Professor-Emeritus of Economics, University of Pennsylvania, is of more than passing interest as an intelligent American's reaction to our National Health Service. It is based largely upon evidence he collected himself during a seven-months' tour of Britain in 1956. On the whole, his facts are sound, he has obviously striven hard to collect points of view from all angles and his sifting of the evidence is pleasantly impartial. To see ourselves as others see us is often salutary. This attractively written book gives us an admirable opportunity to undergo this experience. (Pennsylvania University Press. London: Oxford University Press, price 32*s.*)

Accident Services of Great Britain and Ireland is the interim report of the committee established in 1960 'to keep under continuing review the accident services of Great Britain and Ireland and make recommendations'. The report makes suggestions for the organization of such services, the organization of units and their staffing, and for the training of medical personnel who will take part in the services. (Accident Services Review Committee, B.M.A. House, Tavistock Square, London, W.C.1.)

Elementary Textbook of Anatomy and Physiology Applied to Nursing, by Janet T. E. Riddle, R.G.N., R.F.N., O.N.C.—Nurses will find this a most valuable book. It is brief but very much to the point, easy to read and illustrated by numerous clear and instructive line drawings. Frequent references are made to clinical medicine and nursing procedures and difficult points are made clear by sensible analogies. Important words are heavily printed to assist the reader in revision. It was a pleasure to read this book which can be strongly recommended. (E. & S. Livingstone Ltd., price 12*s.* 6*d.*)

OFFICIAL PUBLICATION

Ageing and the Semi-skilled: A Survey of Manufacturing Industry on Merseyside (M.R.C. Memorandum No. 40), by Alastair Heron and Sheila M. Chown, assisted by M. S. Featherstone and Catherine M. Cunningham, makes a useful contribution to this important subject. Twenty-three firms cooperated in the inquiry which was based on information elicited from managers and supervisors and on a study of the jobs actually done by the semi-skilled workers in each. The age of 40 was selected as the point at which a man became an 'older worker'. There was general agreement that the performance of older workers tends to decrease and they become slower, but that this is off-set by greater dependability, experience and loyalty. 'Alternative work' suitable for workmen who are getting on in years tends to be rather narrowly confined to such tasks as sweeping and cleaning except in rare instances in which specialized knowledge and experience can be put to use. Pointing out that it is not easy for older semi-skilled men to change their jobs, even if they accept the resulting drop in earnings and status, the report stresses their need to be 'helped to adapt to a changing industrial situation'. The need for transfer from physically heavy work is often obvious but, the report says, there is apt to be little recognition of the fact that work making a constant demand for speed or for close supervision is probably also unsuitable. Whilst possibilities for retraining are limited the report suggests that industry should look into this question in relation to the special needs of the semi-skilled worker in the second half of his working life. (H.M. Stationery Office, price 5*s.*)

NOTES FROM THE CONTINENT

A European Newsletter

FRANCE

Foot and mouth disease in man?—Professor Verge, Director of the Alfort Central Laboratory for Veterinary Research, raises once again the question of the transmissibility of foot and mouth disease to man. The virus which causes the illness is one of the smallest known, and of the seven distinct varieties three are endemic in France. Whilst many reports have suggested that man may be infected by the virus there has never been any properly controlled series of experiments designed to support or refute this view. Professor Verge draws attention to the fact that new employees at his laboratory often suffer an influenza-like illness within a few days of coming into contact with foot and mouth disease for the first time, but he has been unable to demonstrate any serological evidence that incriminates the virus. Complement fixation, the presence of specific antibodies, together with other tests commonly used to identify infectious diseases, have all proved negative and it has been impossible so far to transmit the disease from humans to susceptible animals. Concluding that foot and mouth disease is much less common in man than is usually supposed, Professor Verge predicts that refinements in virus technology will show clearly that the great majority of cases of human stomatitis are not related in any way to this common and highly contagious disease of cattle.

Oral treatment of diabetes mellitus.—Despite the undoubted value of a combination of the sulphonamides and biguanides in the oral treatment of some cases of diabetes, R. Deuil and his colleagues regard the use of these drugs, especially in young diabetics, with some misgiving. They consider that insulin is still the best treatment for patients under 40 years of age and of less than average weight, even if there is no family history of diabetes or any suggestion of previous ketonuria. On the other hand they find that oral treatment has a useful place in obese patients over the age of 40, but that the efficacy diminishes as the weight approaches the normal figure for the individual patient. With these reservations the authors conclude that oral treatment is appropriate in 'an immense number' of diabetics, a fact largely due to the discovery of the guanidines. They stress the importance of regular supervision of patients receiving oral treatment, the need for proper dietary restrictions, and the liability of those who are overweight to become refractory to this treatment should they lose weight sufficiently. Because sulphonamide-guanidine treatment is not always fully effective they consider that it cannot altogether replace insulin therapy which is the treatment of choice in young patients.

Cirrhosis and urinary output.—The ancient view that one of the most favourable signs in cirrhosis of the liver is the occurrence of a normal diuresis is challenged by N. Bariety and his colleagues who have observed several patients with hepatic ascites in whom this did not apply. In these cases the liver disorder was accompanied by a brisk polyuria which developed after a lengthy history of ascites when all the evidence, both clinical and biochemical, pointed to serious liver damage. Far from bringing about an expected improvement the increase in urinary volume seemed to be the beginning of a rapid deterioration ending with the death of the patients. The authors emphasize that such polyuria should not be regarded as a hopeful prognostic sign in every case, for in cirrhotic ascites the rate of sodium excretion is more important than the volume of the urine produced.

Peritoneal biopsy.—Drawing attention to the recent revival of interest in abdominal endoscopy, C. Debray and his colleagues point out that there are occasions when useful information can be obtained by this procedure. Punch biopsy is performed by one instrument under visual control through a second, and although this involves two separate points of entry into the abdominal cavity the authors say that the method has great advantages. Not only can access be obtained to remote parts of the peritoneum but it is also possible, for example, to divide adhesions within the peritoneal cavity under direct vision and even to control various photographic procedures. According to the authors this method greatly facilitates the diagnosis of tuberculous peritonitis and carcinomatosis of the peritoneum as well as a number of liver diseases in which biopsy may be of crucial importance.

Non-specific prostatitis.—P. Aboulker and his colleagues, referring to this 'relatively rare' disorder, describe non-specific prostatitis as a disease of elderly patients, gradual in onset and especially apt to be mistaken for a malignant condition. The chronic inflammatory reaction within the substance of the gland produces in-

durated nodules or a more general hardening which may be difficult to distinguish from tuberculous involvement or carcinoma. Pointing out that even histological examination of the diseased gland may occasionally mislead the pathologist unless he is familiar with the picture of chronic prostatitis, the authors draw attention to the need to consider non-specific prostatitis, with its favourable prognosis, as part of the differential diagnosis in all cases. This is especially important when it is remembered that a prolonged regime of treatment for tuberculous or malignant prostatic disease may be a consequence of an error of diagnosis.

Angina pectoris and hiatus hernia.—A hundred patients with hiatus hernia were studied by P. Hillemand and his colleagues in an attempt to discover whether this condition could be regarded as one of the possible causes of angina pectoris. Not only was the inquiry directed to the question whether angina-like pain could be simulated by a hernia, but also to whether electrocardiographic changes could assist the diagnosis. Another matter of importance was the possibility of curing certain patients with angina by treating their hernia effectively. After analysis of their results statistically, together with a consideration of the clinical and experimental evidence, the authors conclude that hiatus hernia plays little, if any, part in the production of anginal pain which, in the absence of other cardiovascular causes, is most often due to coronary arteriosclerosis.

ITALY

TOURISTS from all over the world have been flocking to Turin this year to attend the celebrations of the first centenary of Italian unity. Among the many congresses and conferences held in association with these celebrations was the Fourth International Medical and Surgical Congress. During the meetings of the Congress, which extended from June 3 to 13, numerous symposia were organized, dealing with a wide range of subjects. Some of the more interesting topics discussed at these are summarized in our 'Notes' this month.

Radiation and hypersensitivity to antigens.—At the international symposium on high-voltage radiotherapy F. Picotti and his colleagues reported on an investigation to study the possible effect of radiation on delayed hypersensitivity to various antigens. Using guinea-pigs with experimentally produced hypersensitivity to antigens such as diphtheria toxoid, egg albumen and gamma globulin, they found that in those inoculated with one antigen there was only slow tissue reaction on the twelfth day of the investigation in those previously irradiated, whereas in those which had not been irradiated there was a strong reaction. This showed that ionizing radiations inhibit the production of antibodies. Results in animals inoculated with two antigens were less marked. Irradiation limited to the part of the skin used for the test did not modify the tissue reaction.

Facial epidermoid cysts.—In a paper read before the conference on plastic surgery, G. Francesconi reported upon the clinical and histological study of eleven patients with facial epidermoid cysts. His conclusion was that such congenital malformations are due to a disturbance at a very early stage in development. The fragments of epidermis could be part of the deep mesenchymal structures, giving place to cysts possessing the same characteristics as the skin. Further evidence of this is the fact that such cysts are found more often in cases of breech presentation, in which embryonic development is more complex.

Graft from ear to trachea.—In another paper read before this conference, V. Consiglio and V. Caputo reported on the successful repair of partial loss of the wall of the trachea using cartilage taken from the patient's ear. The tissue of the donor site was considered to be particularly suitable for the purpose, being similar to that which it was to replace: plastic yet firm, and 'biologically suitable'. The only complication was the occurrence of emphysema which was 'easily controlled' within forty-eight hours and which was attributed to a 'slight imperfection' in joining the edge of the graft to the trachea.

The 'new look' in textbooks.—Much interest has been aroused by the publication of a textbook of cardiology, complete with records of heart sounds and murmurs. Known as a 'phonotexte', the idea is that, having read all about 'heart sounds and murmurs', the reader can then play the records and hear the sounds and murmurs for himself. Some of the records are 'slow action ones', so that the reader-listener has every opportunity to analyse the components of the sounds and murmurs and their time-relationships.

'Notes from the Continent' are produced in collaboration with the Editors of *Bruxelles-Médical* (Belgium), *Le Concours Médical* (France), *Münchener Medizinische Wochenschrift* (Germany), and *Minerva Medica* (*Italy*).

THE PRACTITIONER

Fifty Years Ago

OCTOBER 1911

'There is occasions and causes why and wherefore in all things'.—Shakespeare: *King Henry V*, v.1.3.

THE issue opens with a flourish of Knights: Sir Robert W. Burnet, M.D., F.R.C.P., J.P., Physician to His Majesty's Household; Consulting Physician to the Great Northern Central Hospital, on 'Flatulence'; Sir Frederick Wallis, F.R.C.S., Surgeon to Charing Cross Hospital,

Sir George Harold Arthur Comyns Berkeley, M.D., M.C., F.R.C.P., F.R.C.S., F.R.C.O.G. (1865-1946)

etc., on 'Pruritus Ani'; Sir John F. H. Broadbent, M.D., F.R.C.P., Physician to Outpatients, St. Mary's Hospital; Assistant Physician to the London Fever Hospital; Physician to the Hampstead General Hospital, etc., on 'Measles'; and Sir Lambert H. Ormsby, M.D., F.R.C.S., Senior Surgeon to the Meath Hospital, and County Dublin Infirmary; Senior Surgeon to the National Children's Hospital, Dublin, on 'Burns and Scalds'.

In the treatment of flatulence, Sir Robert Burnet considers that 'Tea must be limited in quantity and must be freshly made. The stewed decoction called tea, so dear to the heart of the hospital outpatient, is a fruitful source of these digestive troubles and of the "spasms" so graphically described by the frequenters of hospital outpatient rooms'. He adds: 'Distension and disturbances of digestion are not, however, by any means confined to the class of persons who come under treatment at hospitals, and as a source of flatulence the excessive use of tea amongst well-to-do people should always be borne in mind'.

Sir John Broadbent concludes his article on 'Measles' by saying that 'Good nursing is of the greatest importance. Drugs are seldom required except for complications, which must be suitably treated as they arise. For healthy children properly cared for in good homes an attack of measles for the most part runs a normal course and does not give rise to serious anxiety or call for special treatment'.

In 'Burns and Scalds', Sir Lambert H. Orsmby says that if severe shock has been diagnosed there is only one treatment. 'Without wasting time or increasing shock by difficult attempts at the taking off of clothes . . . the patient is placed in a bath of normal saline of about 98-100°F. and having been unclothed is kept there for hours . . . until the pulse temperature and general condition show fairly clearly that the vaso-motor centre is regaining its accustomed control'.

In an article on 'Dysmenorrhœa', G. F. Blacker, M.D., F.R.C.P., F.R.C.S., Obstetric Physician to University College Hospital and the Great Northern Central Hospital; Teacher of Gynæcology at the Royal Army Medical College, etc., expresses the opinion that 'at the present day the necessity for some form of pleasant exercise in the open air does not require so much advocacy as was formerly the case, for the tendency of the modern girl to play games of all sorts renders this advice often superfluous. Care must, however, be taken to guard against excess in this direction. The habit of playing golf, hockey, or tennis during the periods must be deprecated, and in any case where the pain is severe such a danger must be guarded against by confining the patient, if possible, rigorously to bed'.

'The symptom of "backache" in women', writes Comyns Berkeley, M.D., F.R.C.P., Obstetrician and Gynæcologist to Middlesex

Hospital; Surgeon to Inpatients, Chelsea Hospital for Women, etc., 'strikingly resembles the cry of "Wolf" in the fable, inasmuch as it is so often complained of with *apparently* so little cause, and consequently there is a danger of the practitioner overlooking some serious lesion from a too cursory examination'. Dealing with coccydynia, he comments: 'Just as there is fashion in women's dress, so there is fashion in women's disease, and whereas a few years ago the coccyx was being discussed, written about, and operated upon, now, apart from definite injury, the local treatment of coccydynia has become almost a thing of the past'.

Born in 1856, George Harold Arthur Comyns Berkeley was educated at Dulwich, Marlborough, and Cambridge before going to the Middlesex Hospital in 1888. During his long association with the Middlesex and with the Chelsea Hospital for Women he showed himself a worthy successor to his preceptor, Bland-Sutton. A careful operator, he was insistent on strict asepsis, and taught that obstetric mishaps arose chiefly through ignorance, carelessness, and undue haste. In addition to his hospital teaching, he exerted tremendous influence as an examiner, through his editorship of the *Journal of Obstetrics and Gynæcology of the British Empire*, and his contributions to the famous 'Ten Teachers' 'Midwifery' and 'Gynæcology'. With his colleague, Victor Bonney, he brought team work almost to perfection, their Wertheim operations alone numbering close on 400. Their wealth of experience was reflected in the 'Textbook of Gynæcological Surgery'. Berkeley's interest in nursing was evidenced by the books he wrote on the subject which were standard works for thirty years, and by his part in the foundation of the Royal College of Nursing. Knighted in 1934, he was a Fellow of the Colleges of Physicians, Surgeons, and Obstetricians and Gynæcologists. Despite heavy professional commitments he golfed, hunted, and attended the smoking concerts so dear to one of his genial and humorous nature.

'The essential cause of morbid blushing', according to Harry Campbell, M.D., F.R.C.P., Physician to the West London Hospital for Nervous Diseases, 'is an inherited morbid temperament'. He stresses that sensitive people 'are met with in the most unlooked-for places. . . . Sensitive persons may be found among the chimney sweeps and the slaughterers, nay, the very hangman himself may be acutely sensitive, so effectually may the force of circumstances override temperamental unfitness'.

Although 'the *bromides* easily hold first place' in the treatment of epilepsy, George Johnston, M.D., M.R.C.P., Physician to the Hospital for Epilepsy and Paralysis, Maida Vale, London, etc., gives a list of other drugs which 'may be tried', and often with success when bromides alone are found insufficient to control the seizures. Among these he lists tincture of digitalis which 'has been found of service in many cases of epilepsy, and it is particularly useful in the nocturnal form, where a dose of from 5 to 10 minims may be given with the dose of bromide at bedtime'.

T. H. B.

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